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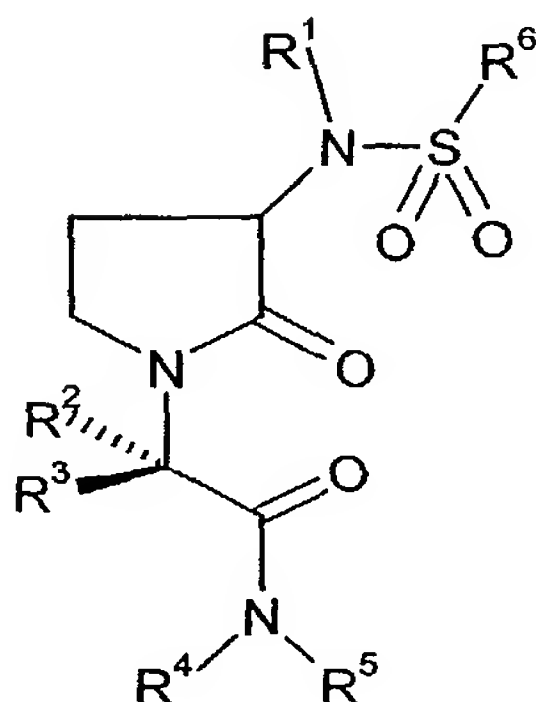
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(54) Title: PYRROLIDIN-2-ONE DERIVATIVES AS INHIBITORS OF FACTOR XA

(57) Abstract: The invention relates to compounds of formula (Ic) processes for their preparation, pharmaceutical compositions containing them and to their use in medicine, particularly use in the amelioration of a clinical condition for which a Factor Xa inhibitor is indicated.



(Ic)



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PYRROLIDIN-2-ONE DERIVATIVES AS INHIBITORS OF FACTOR XA

Field of the Invention

5 The present invention relates to a novel class of chemical compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, particularly use in the amelioration of a clinical condition for which a Factor Xa inhibitor is indicated.

Background of the Invention

Factor Xa is a member of the trypsin-like serine protease class of enzymes. It is a key enzyme in the coagulation cascade. A one-to-one binding of Factors Xa and Va with calcium ions and phospholipid converts prothrombin into thrombin. Thrombin plays a central role in
15 the mechanism of blood coagulation by converting the soluble plasma protein, fibrinogen, into insoluble fibrin. The insoluble fibrin matrix is required for the stabilisation of the primary hemostatic plug. Many significant disease states are related to abnormal hemostasis. With respect to the coronary arterial vasculature, abnormal thrombus formation due to the rupture of an established atherosclerotic plaque is the major cause of acute myocardial infarction
20 and unstable angina. Both treatment of an occlusive coronary thrombus by thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) are often accompanied by an acute thrombotic reclosure of the affected vessel which requires immediate resolution. With respect to the venous vasculature, a high percentage of patients undergoing major surgery in the lower extremities or the abdominal area suffer from thrombus formation in the
25 venous vasculature which can result in reduced blood flow to the affected extremity and a pre-disposition to pulmonary embolism. Disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer and is characterised by the rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout
30 the vasculature leading to widespread organ failure.

Beyond its direct role in the formation of fibrin rich blood clots, thrombin has been reported to have profound bioregulatory effects on a number of cellular components within the vasculature and blood, (Shuman, M.A., Ann. NY Acad. Sci., 405: 349 (1986)).

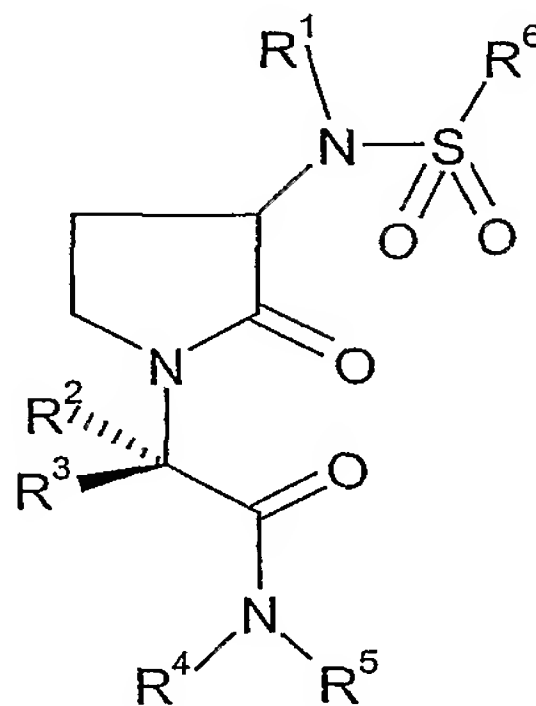
35 A Factor Xa inhibitor may be useful in the treatment of acute vascular diseases such as coronary thrombosis (for example myocardial infarction and unstable angina), thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty, transient ischemic attacks, pulmonary
40 embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal

narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke. They may also have utility as anti-coagulant agents both in-vivo and ex-vivo, and in oedema and inflammation. Thrombin has been reported to contribute to lung fibroblast proliferation, thus, Factor Xa inhibitors could be useful for the treatment of some
 5 pulmonary fibrotic diseases. Factor Xa inhibitors could also be useful in the treatment of tumour metastasis, preventing the fibrin deposition and metastasis caused by the inappropriate activation of Factor Xa by cysteine proteinases produced by certain tumour cells. Thrombin can induce neurite retraction and thus Factor Xa inhibitors may have potential in neurogenerative diseases such as Parkinson's and Alzheimer's disease. They
 10 have also been reported for use in conjunction with thrombolytic agents, thus permitting the use of a lower dose of thrombolytic agent.

The present invention provides novel Factor Xa inhibitors. Compounds of the present invention have oral bioavailability and PK profiles suitable for acute and chronic therapies.
 15

Summary of the Invention

The present invention provides compounds of formula (Ic):



(Ic)

wherein:

R¹ represents hydrogen, -C₁₋₆alkyl, -C₃₋₆alkenyl, -C₃₋₆alkynyl, -C₂₋₃alkylOH, -C₂₋₃alkylNR^bR^a, -C₂₋₃alkylNHCOR^a, -C₂₋₃alkylNHCO₂R^b, -C₂₋₃alkylNHHSO₂R^b, -C₂₋₃alkylNHCONR^bR^c, -C₂₋₃alkyl
 25 OCONR^bR^c, -C₂₋₃alkylOC₁₋₆alkyl, -C₂₋₃alkylOCH₂phenyl, phenyl or 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH, or R¹ represents a group X-W;
 30 X represents -C₁₋₃alkylene-, propenylene, propynylene;

W represents -CN, -CO₂H, -CONR^bR^c, -COC₁₋₆alkyl, -CO₂C₁₋₆alkyl, -CO₂C₃₋₆alkenyl, phenyl or 5- or 6- membered aromatic or non-aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic or non-aromatic heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;

R^a represents hydrogen, -C₁₋₃alkyl, phenyl or a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;

R^b and R^c independently represent hydrogen or -C₁₋₄alkyl;

R² and R³ independently represent hydrogen, -C₁₋₃alkyl or -CF₃, with the proviso that one of R² and R³ is -C₁₋₃alkyl or -CF₃ and the other is hydrogen;

R⁴ and R⁵, together with the N atom to which they are bonded, form a 4-, 5-, 6-, 7- or 8-membered non-aromatic heterocyclic ring, bridged or unbridged, optionally containing an additional heteroatom selected from O, N or S, and optionally substituted by:

(i) one or more substituents selected from: -NH₂, -CF₃, F, -OH, =O, -CO₂H, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₁₋₆alkylOH, -(C₁₋₃alkyl)NR^bR^c, -(C₀₋₃alkyl)CONR^bR^c, -NHSO₂CF₃, -NHSO₂(C₀₋₃alkyl)R^a, -NHCH₂COCH₂O(C₁₋₃alkyl), -(C₀₋₃alkyl)CO₂C₁₋₄alkyl, -CONHC₂₋₃alkylOH, -CH₂NHC₂₋₃alkylOH, -CH₂OC₁₋₃alkyl, -COCH₂NR^bR^c, -COCH₂N⁺(CH₃)₃ and -CH₂SO₂C₁₋₃alkyl;

(ii) a group -NHCOR^d or -NR^bR^d,

R^d represents -C₁₋₆alkyl, -C₂₋₆alkynyl, -C₁₋₆alkoxy, -C₁₋₆alkylOH, -C₁₋₃alkylCO₂H, -C₁₋₃alkylNR^bR^c, -C₁₋₃alkylCO₂C₁₋₃alkyl, -C₁₋₃alkylCONR^bR^c and -C₁₋₃alkylOC₁₋₃alkyl;

(iii) a group -Y-R^e,

Y represents -C₁₋₃alkylene-, -NHCO-, -NHCO₂C₁₋₃alkylene-, -NHC₁₋₃alkylene-, -CO-, -C₁₋₃alkylNH-, -C₁₋₃alkylNHCO-, -C₁₋₃alkylNHCO₂-, -CH₂NHSO₂CH₂- or a direct link,

R^e represents phenyl, a 5- or 6- membered heterocycle containing at least one heteroatom selected from O, N or S, or a 5- or 6- membered cycloalkyl, each of which is optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH; or

(iv) a second ring R^f which is fused to the non-aromatic heterocyclic ring formed by R⁴ and R⁵, wherein R^f represents phenyl, a 5- or 6- membered cycloalkyl group or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, and the fused bicyclic group is optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;

with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is - NH_2 , -OH, - C_{1-6} alkoxy, - $NHSO_2CF_3$, - $NHSO_2(C_{0-3}alkyl)R^a$, - $NHCOR^d$, - NR^bR^d , - $NHCOR^e$, - $NHCO_2C_{1-3}alkyleneR^e$ or - $NHC_{1-3}alkyleneR^e$, - $NHCH_2COCH_2O(C_{1-3}alkyl)$, the substituent is
 5 not attached to a ring carbon atom adjacent to a heteroatom;

R^6 represents:

- (i) a fused bicyclic group - R^gR^h ;
- (ii) a group - R^g-R^h ;
- 10 (iii) a group - $Z-R^h$ wherein Z represents - $C_{1-3}alkylene$ -, - $C_{2-3}alkenylene$ - or a direct link;

wherein R^g and R^h independently represent phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents
 15 selected from: - $C_{1-3}alkyl$, - $C_{1-3}alkoxy$, halogen, -CN, - CF_3 , - NH_2 , - CO_2H and -OH;
 and pharmaceutically acceptable derivatives thereof.

Further aspects of the invention are:

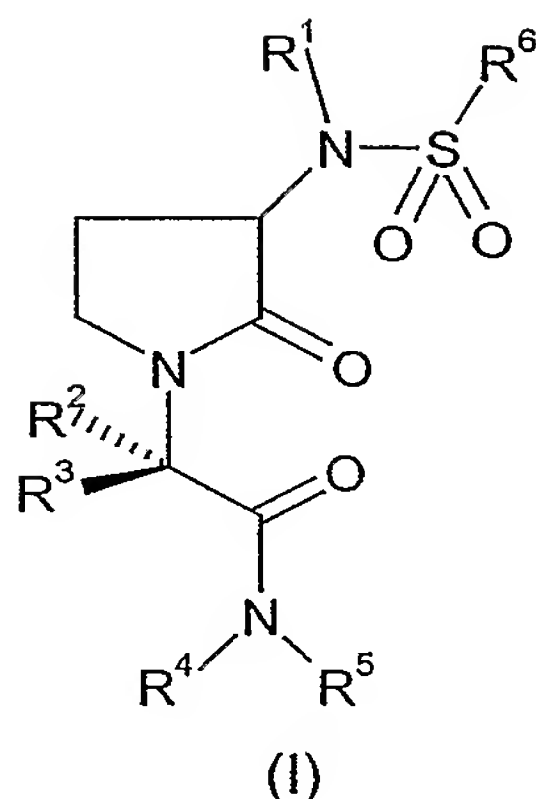
- A pharmaceutical composition comprising a compound of the invention together
 20 with a pharmaceutical carrier and/or excipient.
- A compound of the invention for use in therapy.
- Use of a compound of the invention for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.
- 25 - A method of treating a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor comprising administering a therapeutically effective amount of a compound of the invention.

Detailed Description of the Invention

30

The present invention provides compounds of formula (I):

5



wherein:

5

R^1 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{2-3}$ alkylOH, $-C_{2-3}$ alkylNR^bR^a, $-C_{2-3}$ alkylNHCOR^a, $-C_{2-3}$ alkylNHCO₂R^b, $-C_{2-3}$ alkylNH₂SO₂R^b, $-C_{2-3}$ alkylNHCONR^bR^c, or a group X-W;

X represents $-C_{1-3}$ alkylene-, propenylene, propynylene;

10 W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl, $-CO_2C_{2-6}$ alkenyl, $-OCONR^bR^c$, $-OC_{1-6}$ alkyl, $-OCH_2$ phenyl, phenyl or 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-C_{1-3}$ alkylOH, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

15

R^a represents hydrogen, $-C_{1-3}$ alkyl, phenyl or a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or heterocyclic group being optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-C_{1-3}$ alkylOH, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

20

R^b and R^c independently represent hydrogen or $-C_{1-3}$ alkyl;

R^2 and R^3 independently represent hydrogen, $-C_{1-3}$ alkyl or $-CF_3$, with the proviso that when one of R^2 and R^3 is $-C_{1-3}$ alkyl or $-CF_3$, the other is hydrogen;

25

R^4 and R^5 , together with the N atom to which they are bonded, form a 5-, 6- or 7- membered non-aromatic heterocyclic ring, bridged or unbridged, optionally containing an additional heteroatom selected from O, N or S, and optionally substituted by: (i) one or more substituents selected from: $-NH_2$, $-CF_3$, F, $-OH$, $=O$, $-CO_2H$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-C_{1-6}$ alkylOH, $-(C_{1-3}alkyl)NR^bR^c$, $-(C_{0-3}alkyl)CONR^bR^c$, $-NHSO_2CF_3$, $-NHSO_2(C_{0-3}alkyl)R^a$ and $-(C_{0-3}alkyl)CO_2C_{1-3}alkyl$;

30

(ii) a group -NHCOR^d or $\text{-NR}^b\text{R}^d$,

R^d represents $\text{-C}_{1-6}\text{alkyl}$, $\text{-C}_{2-6}\text{alkynyl}$, $\text{-C}_{1-6}\text{alkoxy}$, $\text{-C}_{1-6}\text{alkylOH}$, $\text{-C}_{1-3}\text{alkylCO}_2\text{H}$, $\text{-C}_{1-3}\text{alkylNR}^b\text{R}^c$, $\text{-C}_{1-3}\text{alkylCO}_2\text{C}_{1-3}\text{alkyl}$ or $\text{-C}_{1-3}\text{alkylCONR}^b\text{R}^c$;

(iii) a group -Y-R^e ,

5 Y represents $\text{-C}_{1-3}\text{alkylene-}$, -NHCO- , $\text{-NHCO}_2\text{C}_{1-3}\text{alkylene-}$, $\text{-NHC}_{1-3}\text{alkylene-}$, -CO- , $\text{-C}_{1-3}\text{alkylNH-}$, $\text{-C}_{1-3}\text{alkylNHCO-}$, $\text{-C}_{1-3}\text{alkylNHSO}_2\text{-}$, $\text{-CH}_2\text{NHSO}_2\text{CH}_2\text{-}$ or a direct link,

R^e represents phenyl, a 5- or 6- membered cycloalkyl or a 5- or 6- membered heterocycle containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by one or more substituents selected from: $\text{-C}_{1-3}\text{alkyl}$, $\text{-C}_{1-3}\text{alkoxy}$, $\text{-C}_{1-3}\text{alkylOH}$,

10 halogen, -CN , -CF_3 , -NH_2 , $\text{-CO}_2\text{H}$ and -OH ; or

(iv) a second ring R^f which is fused to the non-aromatic heterocyclic ring formed by R^4 and R^5 , wherein R^f represents phenyl, a 5- or 6- membered cycloalkyl group or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, and the fused bicyclic group is optionally substituted by one or more substituents
15 selected from: $\text{-C}_{1-3}\text{alkyl}$, $\text{-C}_{1-3}\text{alkoxy}$, $\text{-C}_{1-3}\text{alkylOH}$, halogen, -CN , -CF_3 , -NH_2 , $\text{-CO}_2\text{H}$ and -OH ;

with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is -NH_2 , -OH , $\text{-C}_{1-6}\text{alkoxy}$, $\text{-NHSO}_2\text{CF}_3$, $\text{-NHSO}_2(\text{C}_{0-3}\text{alkyl})\text{R}^a$, -NHCOR^d , $\text{-NR}^b\text{R}^d$, -NHCOR^e , $\text{-NHCO}_2\text{C}_{1-3}\text{alkyleneR}^e$ or $\text{-NHC}_{1-3}\text{alkyleneR}^e$, the substituent is not attached to a ring carbon

20 atom adjacent to a heteroatom;

R^6 represents:

(i) a fused bicyclic group $\text{-R}^g\text{R}^h$;

(ii) a group $\text{-R}^g\text{-R}^h$;

25 (iii) a group -Z-R^h wherein Z represents $\text{-C}_{1-3}\text{alkylene-}$, $\text{-C}_{2-3}\text{alkenylene-}$ or a direct link;

wherein R^g and R^h independently represent phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by one or more substituents selected from: $\text{-C}_{1-3}\text{alkyl}$, $\text{-C}_{1-3}\text{alkoxy}$, halogen, -CN , -CF_3 , -NH_2 , $\text{-CO}_2\text{H}$ and -OH ;

30 and pharmaceutically acceptable salts or solvates thereof.

When R^1 represents a group X-W:

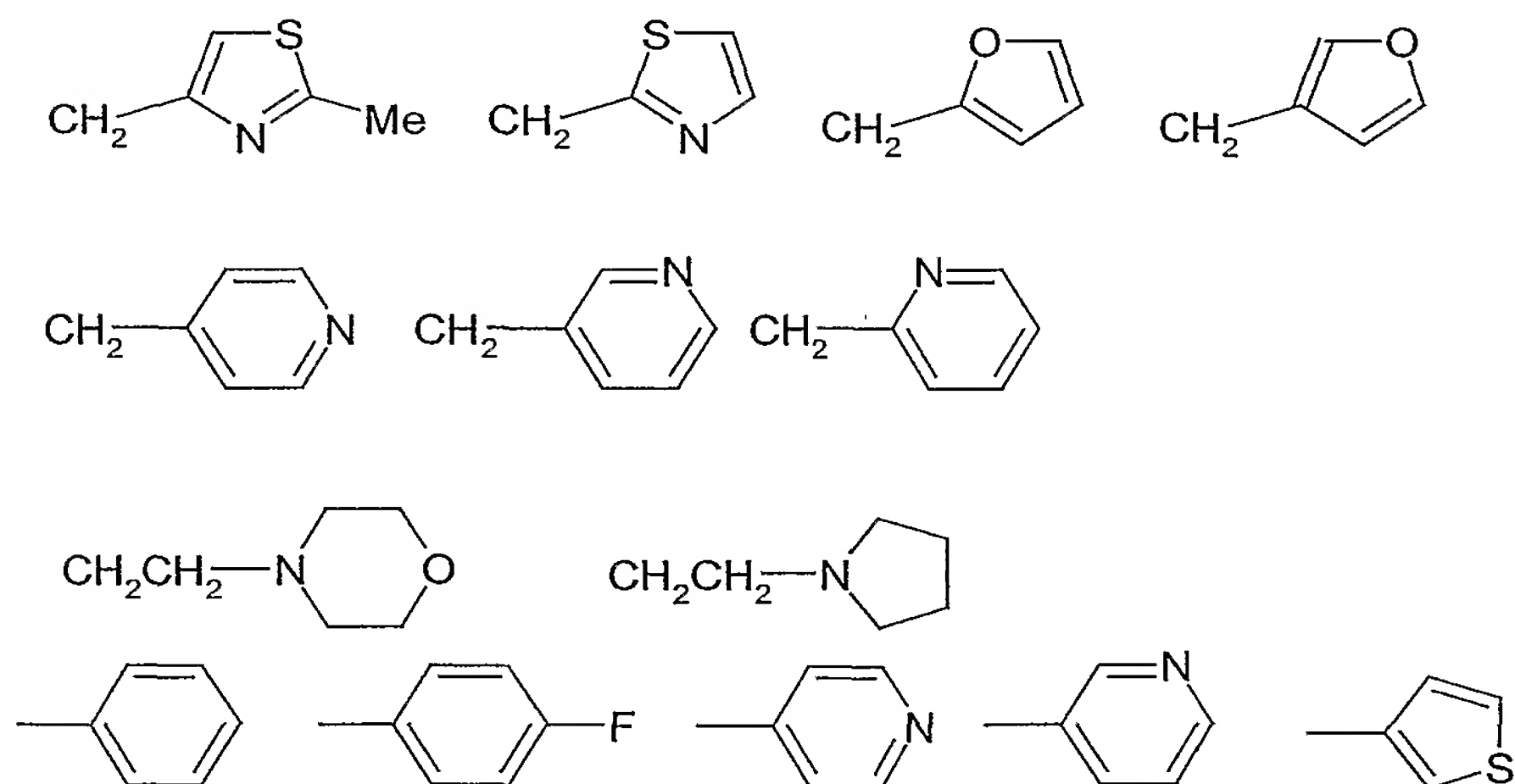
Preferably, X represents $\text{-C}_{1-3}\text{alkylene-}$, more preferably -methylene- .

Preferably, W represents -CN , $\text{-CO}_2\text{H}$, $\text{-CONR}^b\text{R}^c$, $\text{-COC}_{1-6}\text{alkyl}$, $\text{-CO}_2\text{C}_{1-6}\text{alkyl}$ or a 5- or 6-
35 membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S.

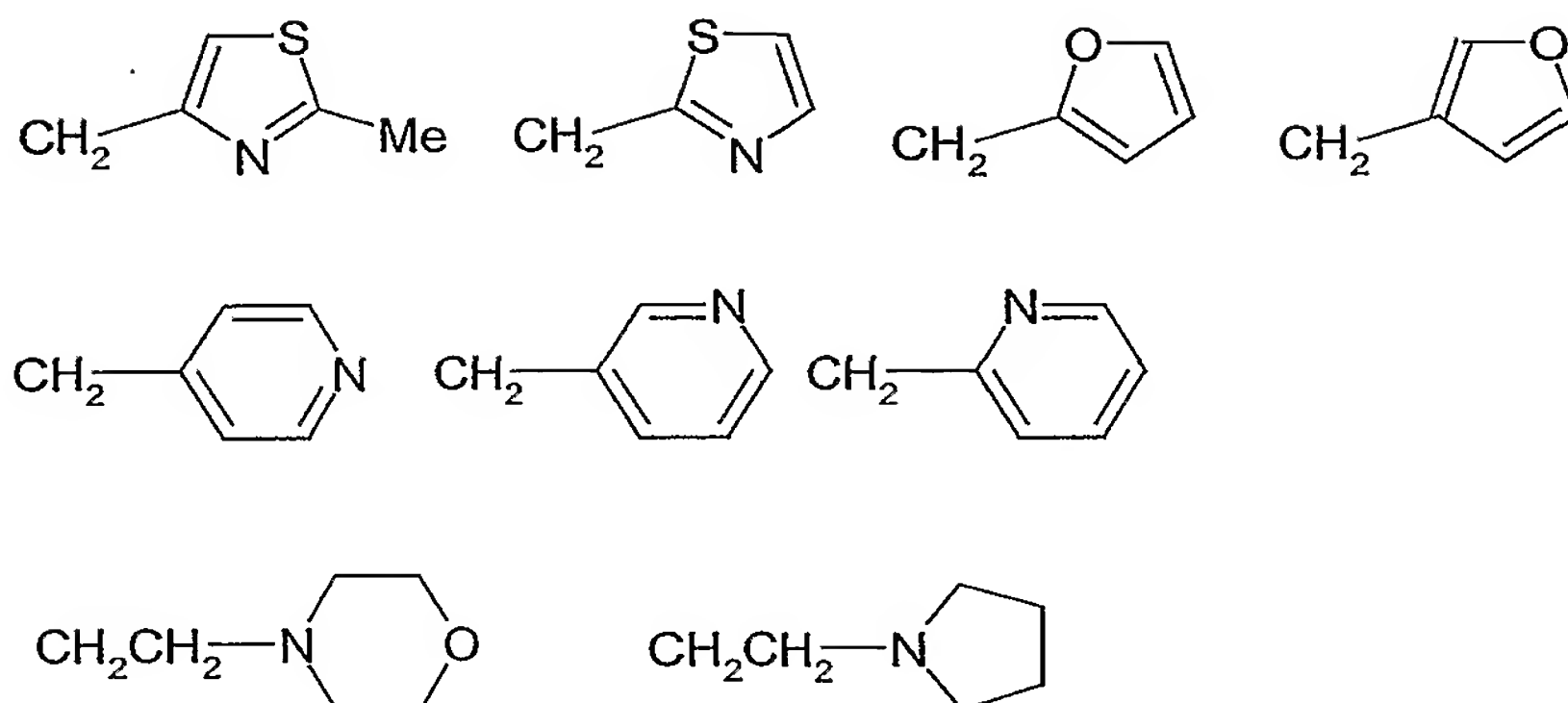
Preferably, R^1 represents hydrogen, $\text{-C}_{1-6}\text{alkyl}$, $\text{-C}_{2-6}\text{alkenyl}$ or a group X-W wherein X represents $\text{-C}_{1-3}\text{alkylene-}$ and W represents -CN , $\text{-CO}_2\text{H}$, $\text{-CONR}^b\text{R}^c$, $\text{-COC}_{1-6}\text{alkyl}$, $\text{-CO}_2\text{C}_{1-}$
40 -6alkyl or a 5- or 6- membered aromatic heterocyclic group containing at least one

heteroatom selected from O, N or S. More preferably, R^1 represents a group selected from hydrogen, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CONH}_2$, $-\text{CH}_2\text{COC}_{1-6}\text{alkyl}$ and $-\text{CH}_2\text{CO}_2\text{C}_{1-6}\text{alkyl}$.

In another preferred aspect, R^1 represents hydrogen, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-6}\text{alkenyl}$, $-\text{C}_{2-3}\text{alkylNR}^b\text{R}^a$, $-\text{C}_{2-3}\text{alkylNHCOR}^a$, phenyl or a 5- or 6- membered aromatic heterocycle, or R^1 represents a group X-W wherein X represents $-\text{C}_{1-3}\text{alkylene-}$ and W represents $-\text{CN}$, $-\text{CO}_2\text{H}$, $-\text{CONR}^b\text{R}^c$, $-\text{COC}_{1-6}\text{alkyl}$, $-\text{CO}_2\text{C}_{1-6}\text{alkyl}$ or a 5- or 6- membered aromatic or non-aromatic heterocyclic group containing at least one heteroatom selected from O, N or S. More preferably, R^1 represents hydrogen, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-6}\text{alkenyl}$, $-\text{C}_{2-3}\text{alkylNR}^b\text{R}^a$, $-\text{C}_{2-3}\text{alkylNHCOR}^a$, or R^1 represents a group X-W wherein X represents $-\text{C}_{1-3}\text{alkylene-}$ and W represents $-\text{CN}$, $-\text{CO}_2\text{H}$, $-\text{CONR}^b\text{R}^c$, $-\text{COC}_{1-6}\text{alkyl}$, $-\text{CO}_2\text{C}_{1-6}\text{alkyl}$ or a 5- or 6- membered aromatic or non-aromatic heterocyclic group containing at least one heteroatom selected from O, N or S. Even more preferably, R^1 represents a group selected from: hydrogen, $-\text{C}_{1-6}\text{alkyl}$, $-\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{NHCOCH}_3$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2\text{t-Butyl}$, $-\text{CH}_2\text{CONH}_2$, $-\text{CH}_2\text{COCH}_2\text{CH}_3$, $-\text{CH}_2\text{Cot-Butyl}$, $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$,



Most preferably, R^1 represents a group selected from: hydrogen, $-\text{C}_{1-6}\text{alkyl}$, $-\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{NHCOCH}_3$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2\text{t-Butyl}$, $-\text{CH}_2\text{CONH}_2$, $-\text{CH}_2\text{COCH}_2\text{CH}_3$, $-\text{CH}_2\text{Cot-Butyl}$,



In another preferred aspect, R^1 represents a group selected from hydrogen, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CONH}_2$, $-\text{CH}_2\text{COC}_{1-6}\text{alkyl}$ and $-\text{CH}_2\text{CO}_2\text{C}_{1-6}\text{alkyl}$.

5

Preferably, R^2 represents $-\text{C}_{1-3}\text{alkyl}$ or hydrogen, more preferably methyl or hydrogen.

Preferably, R^3 represents $-\text{C}_{1-3}\text{alkyl}$ or hydrogen, more preferably methyl or hydrogen.

10 When the 5-, 6- or 7- membered non-aromatic heterocyclic ring formed by R^4 and R^5 , optionally containing an additional heteroatom, is substituted by one or more substituents selected from group (i):

preferably, the substituents in group (i) are $-\text{NH}_2$, $-\text{CF}_3$, $-\text{OH}$, $-\text{CO}_2\text{H}$, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{alkoxy}$, $-\text{C}_{1-6}\text{alkylOH}$, $-(\text{C}_{1-3}\text{alkyl})\text{NR}^b\text{R}^c$, $-(\text{C}_{0-3}\text{alkyl})\text{CONR}^b\text{R}^c$ and $-\text{NHSO}_2\text{CF}_3$, more preferably $-\text{NH}_2$,

15 $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{alkylOH}$ and $-(\text{C}_{1-3}\text{alkyl})\text{NR}^b\text{R}^c$.

When, the 5-, 6- or 7- membered non-aromatic heterocyclic ring formed by R^4 and R^5 , optionally containing an additional heteroatom, is substituted $-\text{NHCOR}^d$:

preferably, R^d represents $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{1-3}\text{alkylCO}_2\text{H}$, $-\text{C}_{1-3}\text{alkylINR}^b\text{R}^c$, $-\text{C}_{1-}$

20 $3\text{alkylCO}_2\text{C}_{1-3}\text{alkyl}$, or $-\text{C}_{1-3}\text{alkylCONR}^b\text{R}^c$, more preferably $-\text{C}_{1-3}\text{alkylCO}_2\text{H}$, $-\text{C}_{1-3}\text{alkylINR}^b\text{R}^c$ or $-\text{C}_{1-3}\text{alkylCO}_2\text{C}_{1-3}\text{alkyl}$.

When, the 5-, 6- or 7- membered non-aromatic heterocyclic ring formed by R^4 and R^5 , optionally containing an additional heteroatom, is substituted by $-\text{NR}^b\text{R}^d$:

25 preferably, R^b represents hydrogen;

preferably, R^d represents $-\text{C}_{1-6}\text{alkyl}$ or $-\text{C}_{1-6}\text{alkylOH}$.

When the 5-, 6- or 7- membered non-aromatic heterocyclic ring formed by R^4 and R^5 , optionally containing an additional heteroatom, is substituted by Y-R^e :

preferably, Y represents $-C_{1-3}\text{alkylene-}$, $-\text{NHCO-}$, $-\text{NHCO}_2C_{1-3}\text{alkylene-}$, $-\text{NHC}_{1-3}\text{alkylene-}$ or $-C_{1-3}\text{alkylNHSO}_2-$, more preferably $-C_{1-3}\text{alkylene-}$, $-\text{NHCO-}$ or $-\text{NHC}_{1-3}\text{alkylene-}$, most preferably $-C_{1-3}\text{alkylene-}$;

preferably, R^e represents imidazole, pyrrole, pyrazole, pyridine, pyrimidine, furan, oxazole,
 5 1,2,4-triazole, phenyl or pyrrolidine, more preferably pyrrole, pyrazole, pyridine, pyrimidine, 1,2,4-triazole or pyrrolidine, most preferably pyrrolidine; preferably, R^e is unsubstituted or substituted by $-C_{1-3}\text{alkyl}$, $-\text{NH}_2$ or $-C_{1-3}\text{alkylOH}$. A preferred $Y-R^e$ is $-C_{1-3}\text{alkylene-pyrrolidine}$.

When the 5-, 6- or 7- membered non-aromatic heterocyclic ring formed by R^4 and R^5 ,
 10 optionally containing an additional heteroatom, is substituted by a group (iv):
 preferably, R^f represents cyclohexyl. Preferably, R^f is unsubstituted.

Preferably, R^4 and R^5 , together with the N atom to which they are bonded, form a 5- or 6-
 15 membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom
 selected from O, N or S, and optionally substituted by:

- (i) one or more substituents selected from: $-\text{NH}_2$, $-\text{CF}_3$, $-\text{OH}$, $-\text{CO}_2\text{H}$, $-C_{1-6}\text{alkyl}$, $-C_{1-6}\text{alkoxy}$, $-C_{1-6}\text{alkylOH}$, $-(C_{1-3}\text{alkyl})\text{NR}^b\text{R}^c$, $-(C_{0-3}\text{alkyl})\text{CONR}^b\text{R}^c$ and $-\text{NHSO}_2\text{CF}_3$;
 - (ii) a group $-\text{NHCOR}^d$ wherein R^d represents $-C_{1-6}\text{alkyl}$, $-C_{2-6}\text{alkynyl}$, $-C_{1-3}\text{alkylCO}_2\text{H}$, $-C_{1-3}\text{alkylNR}^b\text{R}^c$, $-C_{1-3}\text{alkylCO}_2C_{1-3}\text{alkyl}$ or $-C_{1-3}\text{alkylCONR}^b\text{R}^c$ or a group $-\text{NHR}^d$ wherein
 20 R^d represents $-C_{1-6}\text{alkyl}$ or $-C_{1-6}\text{alkylOH}$;
 - (iii) a group $-\text{Y-R}^e$, Y represents $-C_{1-3}\text{alkylene-}$, $-\text{NHCO-}$, $-\text{NHCO}_2C_{1-3}\text{alkylene-}$, $-\text{NHC}_{1-3}\text{alkylene-}$ or $-C_{1-3}\text{alkylNHSO}_2$, R^e represents imidazole, pyrrole, pyrazole, pyridine, pyrimidine, furan, oxazole, 1,2,4-triazole, phenyl or pyrrolidine optionally substituted by $-C_{1-3}\text{alkyl}$, $-\text{NH}_2$ or $-C_{1-3}\text{alkylOH}$;
 - (iv) a second ring R^f which is fused to the non-aromatic heterocyclic ring formed by R^4 and R^5 , wherein R^f represents cyclohexyl;
- with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is $-\text{NH}_2$, $-\text{OH}$, $-C_{1-6}\text{alkoxy}$, $-\text{NHSO}_2\text{CF}_3$, $-\text{NHCOR}^d$, $-\text{NR}^b\text{R}^d$, $-\text{NHCOR}^e$, $-\text{NHCO}_2C_{1-3}\text{alkyleneR}^e$ or $-\text{NHC}_{1-3}\text{alkyleneR}^e$, the substituent is not attached to a ring carbon atom adjacent to a
 30 heteroatom. More preferably, R^4 and R^5 , together with the N atom to which they are bonded, represent piperidine, 2-(pyrrolidin-1-ylmethyl)pyrrolidine or morpholine.

In another preferred aspect, R^4 and R^5 , together with the N atom to which they are bonded, form a 4-, 5-, 6-, 7- or 8- membered non-aromatic heterocyclic ring, selected from:
 35 piperidine; pyrrolidine; hexamethyleneimine (homopiperidine); morpholine; thiomorpholine; diazepine; tetrahydro-1,6-naphthyridine; 2-azabicyclo[2.2.1]heptane; 2-oxa-5-azabicyclo[2.2.1]heptane; 3,7-diazabicyclo[3.3.1]nonane; 9-oxa-3,7-diazabicyclo[3.3.1]nonane; 2-azabicyclo[2.2.2]octane; 4,6,7,8-tetrahydro-5H-thieno[3,2-c]azepine;

1,2,5,6-tetrahydropyridine; azetidine; 2,5-dihydro-1H-pyrrole; piperazine; hexahydropyrimidine; tetrahydroquinoline; decahydroquinoline; tetrahydroquinoxaline; dihydroisoindole; tetrahydroisoquinoline; tetrahydro-5H-imidazo[4,5-c]pyridine; 1,3,4,5-tetrahydro-2H-2-benzazepine; 2,5-diazabicyclo[2.2.1]heptane; optionally substituted by:

- 5 (i) one or more substituents selected from: $-\text{NH}_2$, $-\text{CF}_3$, F , $-\text{OH}$, $=\text{O}$, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{alkoxy}$, $-\text{C}_{1-6}\text{alkylOH}$, $-(\text{C}_{1-3}\text{alkyl})\text{NR}^b\text{R}^c$, $-(\text{C}_{0-3}\text{alkyl})\text{CONR}^b\text{R}^c$, $-\text{NH}\text{SO}_2\text{CF}_3$, $-\text{NHCH}_2\text{COCH}_2\text{O}(\text{C}_{1-3}\text{alkyl})$, $-(\text{C}_{0-3}\text{alkyl})\text{CO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{CONHC}_{2-3}\text{alkylOH}$, $-\text{COCH}_2\text{NR}^b\text{R}^c$, $-\text{COCH}_2\text{N}^+(\text{CH}_3)_3$, $-\text{CH}_2\text{OC}_{1-3}\text{alkyl}$ and $-\text{CH}_2\text{SO}_2\text{C}_{1-3}\text{alkyl}$;
 (ii) a group $-\text{NHCOR}^d$ or $-\text{NR}^b\text{R}^d$;
 10 R^d represents $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{1-6}\text{alkylOH}$, $-\text{C}_{1-3}\text{alkylCO}_2\text{H}$, $-\text{C}_{1-3}\text{alkylINR}^b\text{R}^c$, $-\text{C}_{1-3}\text{alkylCO}_2\text{C}_{1-3}\text{alkyl}$, $-\text{C}_{1-3}\text{alkylOC}_{1-3}\text{alkyl}$ and $-\text{C}_{1-3}\text{alkylCONR}^b\text{R}^c$;
 (iii) a group $-\text{Y}-\text{R}^e$,
 Y represents $-\text{C}_{1-3}\text{alkylene-}$, $-\text{NHCO-}$, $-\text{NHC}_{1-3}\text{alkylene-}$, $-\text{NHCO}_2\text{C}_{1-3}\text{alkylene-}$, $-\text{C}_{1-3}\text{alkylNHCO-}$, $-\text{C}_{1-3}\text{alkylNHSO}_2\text{-}$, $-\text{CO-}$ or a direct link,
 15 R^e represents phenyl, pyridine, pyrrole, isoxazole, pyrazole, pyrrolidine, cyclopentyl, triazole, pyrazine, furan, thiazole, imidazole, morpholine, piperazine, pyrimidine, piperidine, each of which is optionally substituted by one or more substituents selected from: $-\text{C}_{1-3}\text{alkyl}$, halogen, $-\text{NH}_2$;
 with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is -
 20 NH_2 , $-\text{OH}$, $-\text{C}_{1-6}\text{alkoxy}$, $-\text{NH}\text{SO}_2\text{CF}_3$, $-\text{NHCOR}^d$, $-\text{NR}^b\text{R}^d$, $-\text{NHCOR}^e$, or $-\text{NHC}_{1-3}\text{alkyleneR}^e$, $-\text{NHCO}_2\text{C}_{1-3}\text{alkyleneR}^e$, $-\text{NHCH}_2\text{COCH}_2\text{O}(\text{C}_{1-3}\text{alkyl})$, the substituent is not attached to a ring carbon atom adjacent to a heteroatom.

More preferably R^4 and R^5 , together with the N atom to which they are bonded, form a 5-, 6-,

- 25 7- or 8- membered non-aromatic heterocyclic ring, selected from: piperidine; pyrrolidine; hexamethyleneimine (homopiperidine); morpholine; thiomorpholine; diazepine; tetrahydro-1,6-naphthyridine; 2-azabicyclo[2.2.1]heptane; 2-oxa-5-azabicyclo[2.2.1]heptane; 3,7-diazabicyclo[3.3.1]nonane; 9-oxa-3,7-diazabicyclo[3.3.1]nonane; 2-azabicyclo[2.2.2]octane; 4,6,7,8-tetrahydro-5H-thieno[3,2-c]azepine; 1,2,5,6-tetrahydropyridine; and optionally
 30 substituted by:
 (i) one or more substituents selected from: $-\text{NH}_2$, $-\text{CF}_3$, F , $-\text{OH}$, $=\text{O}$, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{alkoxy}$, $-\text{C}_{1-6}\text{alkylOH}$, $-(\text{C}_{1-3}\text{alkyl})\text{NR}^b\text{R}^c$, $-(\text{C}_{0-3}\text{alkyl})\text{CO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{COCH}_2\text{NR}^b\text{R}^c$ and $-\text{COCH}_2\text{N}^+(\text{CH}_3)_3$;
 (ii) a group $-\text{NHCOR}^d$ or $-\text{NR}^b\text{R}^d$,
 R^d represents $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{1-6}\text{alkylOH}$, $-\text{C}_{1-3}\text{alkylCO}_2\text{H}$, $-\text{C}_{1-3}\text{alkylINR}^b\text{R}^c$, $-\text{C}_{1-3}\text{alkylCO}_2\text{C}_{1-3}\text{alkyl}$, $-\text{C}_{1-3}\text{alkylOC}_{1-3}\text{alkyl}$ and $-\text{C}_{1-3}\text{alkylCONR}^b\text{R}^c$;
 35 (iii) a group $-\text{Y}-\text{R}^e$,
 Y represents $-\text{C}_{1-3}\text{alkylene-}$, $-\text{NHCO-}$, $-\text{NHC}_{1-3}\text{alkylene-}$, $-\text{NHCO}_2\text{C}_{1-3}\text{alkylene-}$, $-\text{C}_{1-3}\text{alkylNHSO}_2\text{-}$ or a direct link,

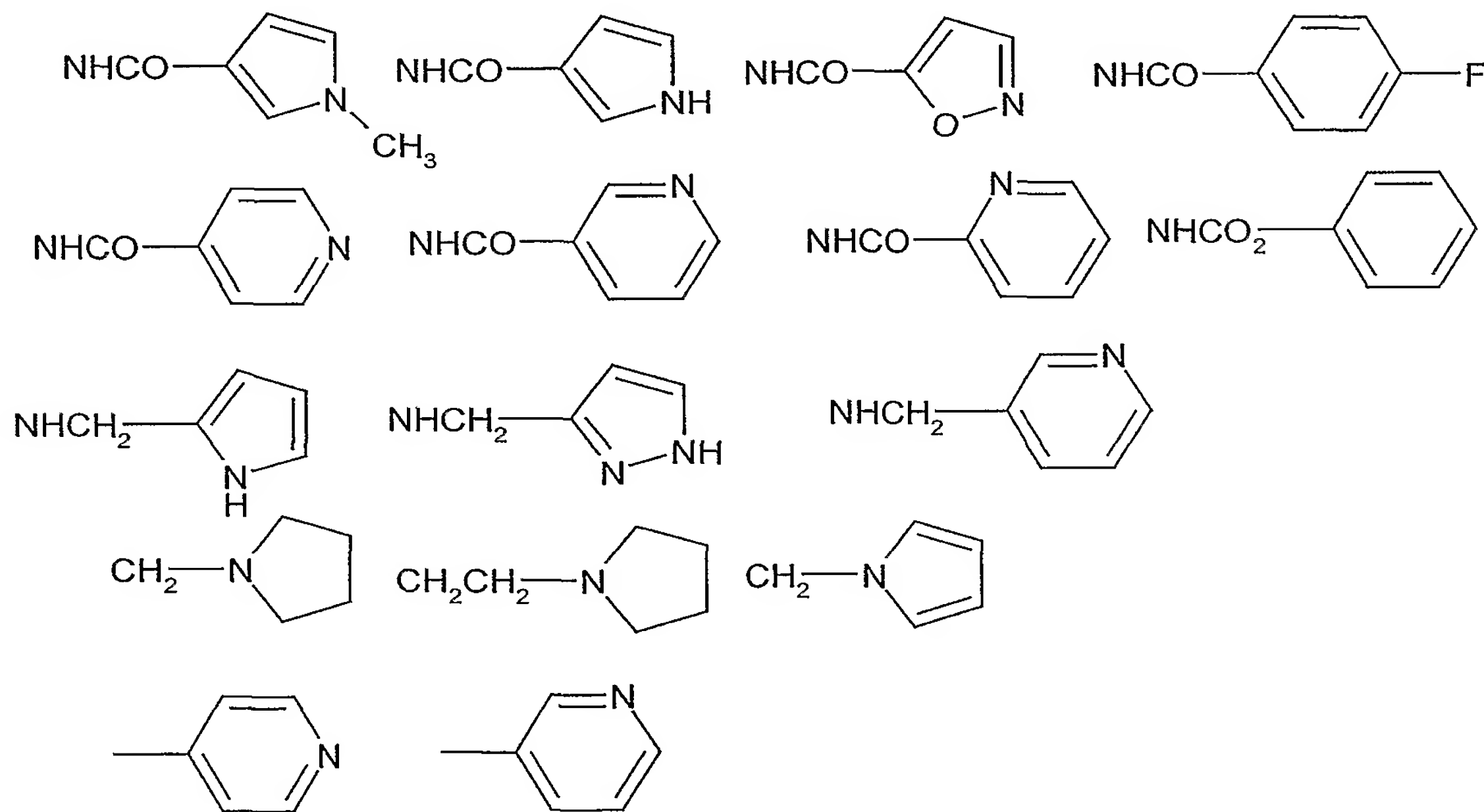
R^e represents phenyl, pyridine, pyrrole, isoxazole, pyrazole, pyrrolidine, cyclopentyl, triazole, pyrazine, furan, thiazole, imidazole, morpholine, piperazine, pyrimidine, each of which is optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, halogen, $-NH_2$; with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is -

5 NH_2 , $-OH$, $-C_{1-6}$ alkoxy, $-NHCOR^d$, $-NR^bR^d$, $-NHCOR^e$, or $-NHC_{1-3}$ alkylene R^e , $-NHCO_2C_{1-3}$ alkylene R^e , the substituent is not attached to a ring carbon atom adjacent to a heteroatom;

Even more preferably R^4 and R^5 , together with the N atom to which they are bonded, form a 5-, 6-, 7-, 8- membered non-aromatic heterocyclic ring, selected from: piperidine; pyrrolidine;

10 hexamethyleneimine (homopiperidine); morpholine; thiomorpholine; diazepine; tetrahydro-1,6-naphthyridine; 2-azabicyclo[2.2.1]heptane; 2-oxa-5-azabicyclo[2.2.1]heptane; 3,7-diazabicyclo[3.3.1]nonane; 9-oxa-3,7-diazabicyclo[3.3.1]nonane; 2-azabicyclo[2.2.2]octane; optionally substituted by a substituent selected from: $-CH_3$, $=O$, $-NH_2$, F, $-CH_2OH$, $-CH_2CH_2NHCH_3$, $-NHCOC_{1-3}$ alkyl, $-NHCOC\equiv CH$, $-NHCOCH_2CH_2CO_2H$; $-NHCOCH_2N(CH_3)_2$, -

15 $NHCOC_{1-3}$ alkyl CO_2CH_3 ,



with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is - NH_2 , $NHCO_2C_{1-3}$ alkylene R^e , $-NHCO-$ or $-NHCH_2-$ the substituent is not attached to a ring carbon atom adjacent to a heteroatom.

When R^6 represents a fused bicyclic group $-R^gR^h$:

Preferably, R^g represents phenyl or thiophene, more preferably phenyl. Preferably, R^g is unsubstituted. When R^g is thiophene, preferably it is attached to the sulphonyl group at the 2-position.

Preferably, R^h represents phenyl. Preferably, R^h is substituted by halogen, more preferably
5 Cl. Preferably, R^h is monosubstituted.

When R^6 represents a group $-R^g-R^h$:

Preferably, R^g represents thiophene or phenyl, more preferably thiophene. Preferably, R^g is
10 unsubstituted. When R^g is thiophene, preferably it is attached to the sulphonyl group at the 2-position.

Preferably, R^h represents thiophene or phenyl, more preferably thiophene. Preferably, R^h is substituted by halogen, more preferably Cl. Preferably, R^h is monosubstituted.

When R^6 represents a group $-Z-R^h$:

15 Preferably, Z represents $-C_{2-3}$ alkenyl-, more preferably $-CH=CH-$.

Preferably, R^h represents phenyl. Preferably, R^h is substituted by halogen, more preferably Cl. Preferably, R^h is monosubstituted.

(iii) In another preferred aspect, R^6 represents:

20 (i) a fused bicyclic group $-R^gR^h$ wherein R^g represents phenyl, thiophene, imidazole, thiazole, pyrrole or furan optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl and R^h represents phenyl or pyridine optionally substituted by one or more substituents selected from: halogen and $-OH$;

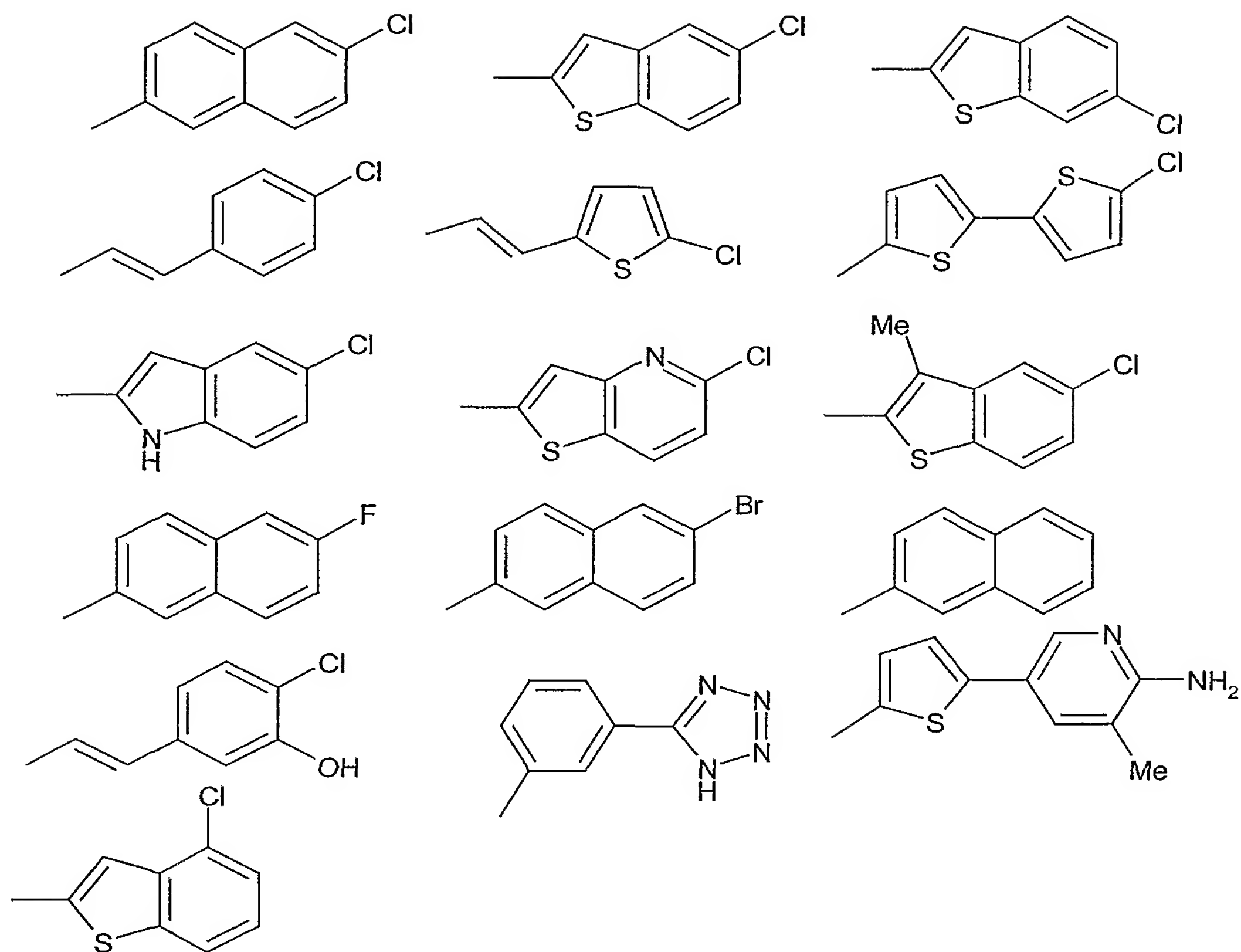
(ii) a group $-R^g-R^h$ wherein R^g represents thiophene or phenyl and R^h represents phenyl,
25 pyridine, thiophene, thiadiazole, tetrazole, isoxazole or furan optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, halogen, $-NH_2$, $-OC_{1-3}$ alkyl and $-OH$;

(iii) a group $-Z-R^h$ wherein Z represents $-C_{2-3}$ alkenylene- or a direct link wherein R^h represents phenyl or thiophene optionally substituted by one or more substituents selected from: halogen, OH and $-CN$;

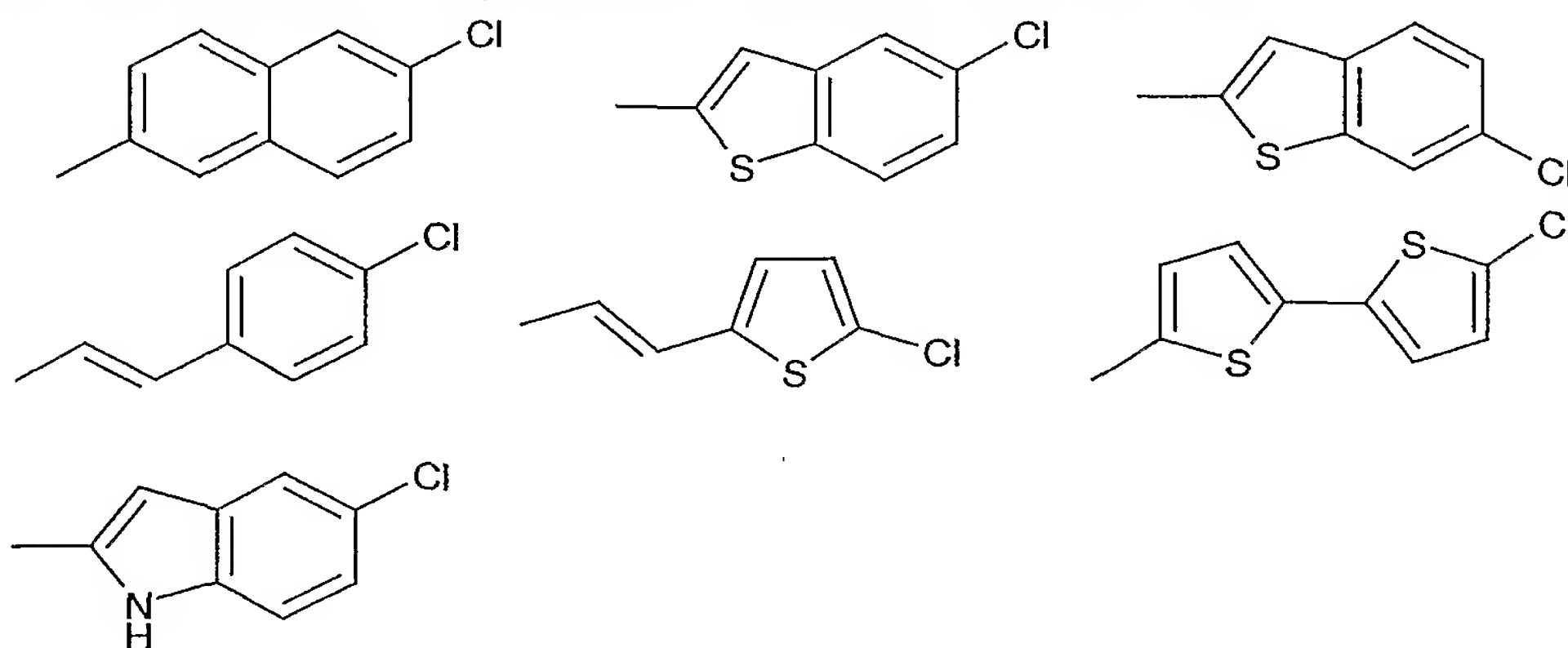
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Preferably, R^6 represents a substituent selected from:

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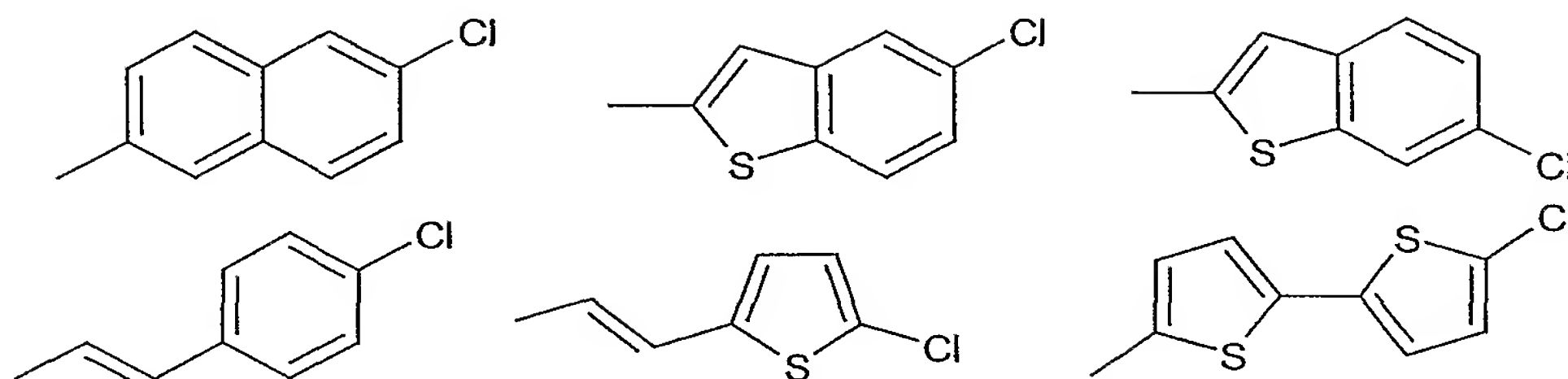


More preferably, R⁶ represents a substituent selected from:



5

Even more preferably, R⁶ represent a substituent selected from:



Most preferably, R^6 represents (chlorothiényl)ethene.

- 5 In another preferred aspect of the invention, R^6 represents chloronaphthylene, chlorobenzothiophene, chlorobisthiophene or chlorophenylethene. More preferably, A represents a group selected from: 6-chloronaphthyl, 5'-chloro-2,2'-bisthiophene, (4-chlorophenyl)ethene, 6-chloro-1-benzothiophene.
- 10 It is to be understood that the present invention covers all combinations of suitable, convenient and preferred groups described hereinabove.

Hence, in a preferred aspect the invention provides compounds of formula (I) wherein:

- R^1 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{3-6}$ alkenyl, $-C_{2-3}$ alkyl NR^bR^a , $-C_{2-3}$ alkyl $NHCOR^a$, phenyl
 15 or a 5- or 6- membered aromatic heterocycle, or R^1 represents a group X-W wherein X represents $-C_{1-3}$ alkylene- and W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl or a 5- or 6- membered aromatic or non-aromatic heterocyclic group containing at least one heteroatom selected from O, N or S.

- R^2 and R^3 independently represent hydrogen, or $-C_{1-3}$ alkyl, with the proviso that one of R^2
 20 and R^3 is $-C_{1-3}$ alkyl and the other is hydrogen;

- R^4 and R^5 , together with the N atom to which they are bonded, form a 4-, 5-, 6-, 7- or 8-
 membered non-aromatic heterocyclic ring, selected from: piperidine; pyrrolidine;
 hexamethyleneimine (homopiperidine); morpholine; thiomorpholine; diazepine; tetrahydro-
 1,6-naphthyridine; 2-azabicyclo[2.2.1]heptane; 2-oxa-5-azabicyclo[2.2.1]heptane; 3,7-
 25 diazabicyclo[3.3.1]nonane; 9-oxa-3,7-diazabicyclo[3.3.1]nonane; 2-azabicyclo[2.2.2]octane;
 4,6,7,8-tetrahydro-5H-thieno[3,2-c]azepine; 1,2,5,6-tetrahydropyridine; azetidine; 2,5-
 dihydro-1H-pyrrole; piperazine; hexahydropyrimidine; tetrahydroquinoline;
 decahydroquinoline; tetrahydroquinoxaline; dihydroisoindole; tetrahydroisoquinoline;
 tetrahydro-5H-imidazo[4,5-c]pyridine; 1,3,4,5-tetrahydro-2H-2-benzazepine; 2,5-
 30 diazabicyclo[2.2.1]heptane; 3,5,6,7-tetrahydro-4H-[1,2,3]triazolo[4,5-b]pyridine; 2,3-dihydro-
 1H-indole; optionally substituted by:

- (i) one or more substituents selected from: $-NH_2$, $-CF_3$, F, $-OH$, $=O$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-C_{1-6}$ alkylOH, $-(C_{1-3}alkyl)NR^bR^c$, $-(C_{0-3}alkyl)CONR^bR^c$, $-NHCH_2COCH_2O(C_{1-3}alkyl)$, $-(C_{0-3}alkyl)CO_2C_{1-4}alkyl$, $-CONHC_{2-3}alkylOH$, $-COCH_2NR^bR^c$, $-COCH_2N^+(CH_3)_3$, $-CH_2OC_{1-3}alkyl$ and $-CH_2SO_2C_{1-3}alkyl$;
- 35

(ii) a group -NHCOR^d or $\text{-NR}^b\text{R}^d$,

R^d represents $\text{-C}_{1-6}\text{alkyl}$, $\text{-C}_{2-6}\text{alkynyl}$, $\text{-C}_{1-6}\text{alkylOH}$, $\text{-C}_{1-3}\text{alkylCO}_2\text{H}$, $\text{-C}_{1-3}\text{alkylINR}^b\text{R}^c$, $\text{-C}_{1-3}\text{alkylCO}_2\text{C}_{1-3}\text{alkyl}$, $\text{-C}_{1-3}\text{alkylOC}_{1-3}\text{alkyl}$ and $\text{-C}_{1-3}\text{alkylCONR}^b\text{R}^c$;

(iii) a group -Y-R^e ,

5 Y represents $\text{-C}_{1-3}\text{alkylene-}$, -NHCO- , $\text{-NHC}_{1-3}\text{alkylene-}$, $\text{-NHCO}_2\text{C}_{1-3}\text{alkylene-}$, $\text{-C}_{1-3}\text{alkylNHCO-}$, $\text{-C}_{1-3}\text{alkylNHSO}_2\text{-}$, $\text{-CH}_2\text{NHSO}_2\text{CH}_2\text{-}$, -CO- or a direct link,

R^e represents phenyl, pyridine, pyrrole, isoxazole, pyrazole, pyrrolidine, cyclopentyl, triazole, pyrazine, furan, thiazole, imidazole, morpholine, piperazine, pyrimidine, piperidine, each of which is optionally substituted by one or more substituents selected from: $\text{-C}_{1-3}\text{alkyl}$,

10 halogen, -NH_2 ;

with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is -NH_2 , -OH , $\text{-C}_{1-6}\text{alkoxy}$, $\text{-NHSO}_2\text{CF}_3$, -NHCOR^d , $\text{-NR}^b\text{R}^d$, -NHCOR^e , or $\text{-NHC}_{1-3}\text{alkyleneR}^e$, $\text{-NHCO}_2\text{C}_{1-3}\text{alkyleneR}^e$, $\text{-NHCH}_2\text{COCH}_2\text{O}(\text{C}_{1-3}\text{alkyl})$, the substituent is not attached to a ring carbon atom adjacent to a heteroatom;

15 R^a represents hydrogen, $\text{-C}_{1-3}\text{alkyl}$, phenyl or a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or heterocyclic group being optionally substituted by one or more substituents selected from: $\text{-C}_{1-3}\text{alkyl}$, $\text{-C}_{1-3}\text{alkoxy}$, $\text{-C}_{1-3}\text{alkylOH}$, halogen, -CN , -CF_3 , -NH_2 , $\text{-CO}_2\text{H}$ and -OH ;

R^b and R^c independently represent hydrogen or $\text{-C}_{1-3}\text{alkyl}$;

20 R^6 represents:

(i) a fused bicyclic group $\text{-R}^g\text{R}^h$ wherein R^g represents phenyl, thiophene, imidazole, thiazole, pyrrole or furan optionally substituted by one or more substituents selected from: $\text{-C}_{1-3}\text{alkyl}$ and R^h represents phenyl or pyridine optionally substituted by one or more substituents selected from: halogen and -OH ;

25 (ii) a group $\text{-R}^g\text{-R}^h$ wherein R^g represents thiophene or phenyl and R^h represents phenyl, pyridine, thiophene, thiadiazole, tetrazole, isoxazole or furan optionally substituted by one or more substituents selected from: $\text{-C}_{1-3}\text{alkyl}$, halogen, -NH_2 , $\text{-OC}_{1-3}\text{alkyl}$ and -OH ;

(iii) a group -Z-R^h wherein Z represents $\text{-C}_{2-3}\text{alkenylene-}$ or a direct link wherein R^h represents phenyl or thiophene optionally substituted by one or more substituents selected

30 from: halogen, OH and -CN ;

and pharmaceutically acceptable salts or solvates thereof.

In a more preferred aspect the invention provides compounds of formula (I) wherein:

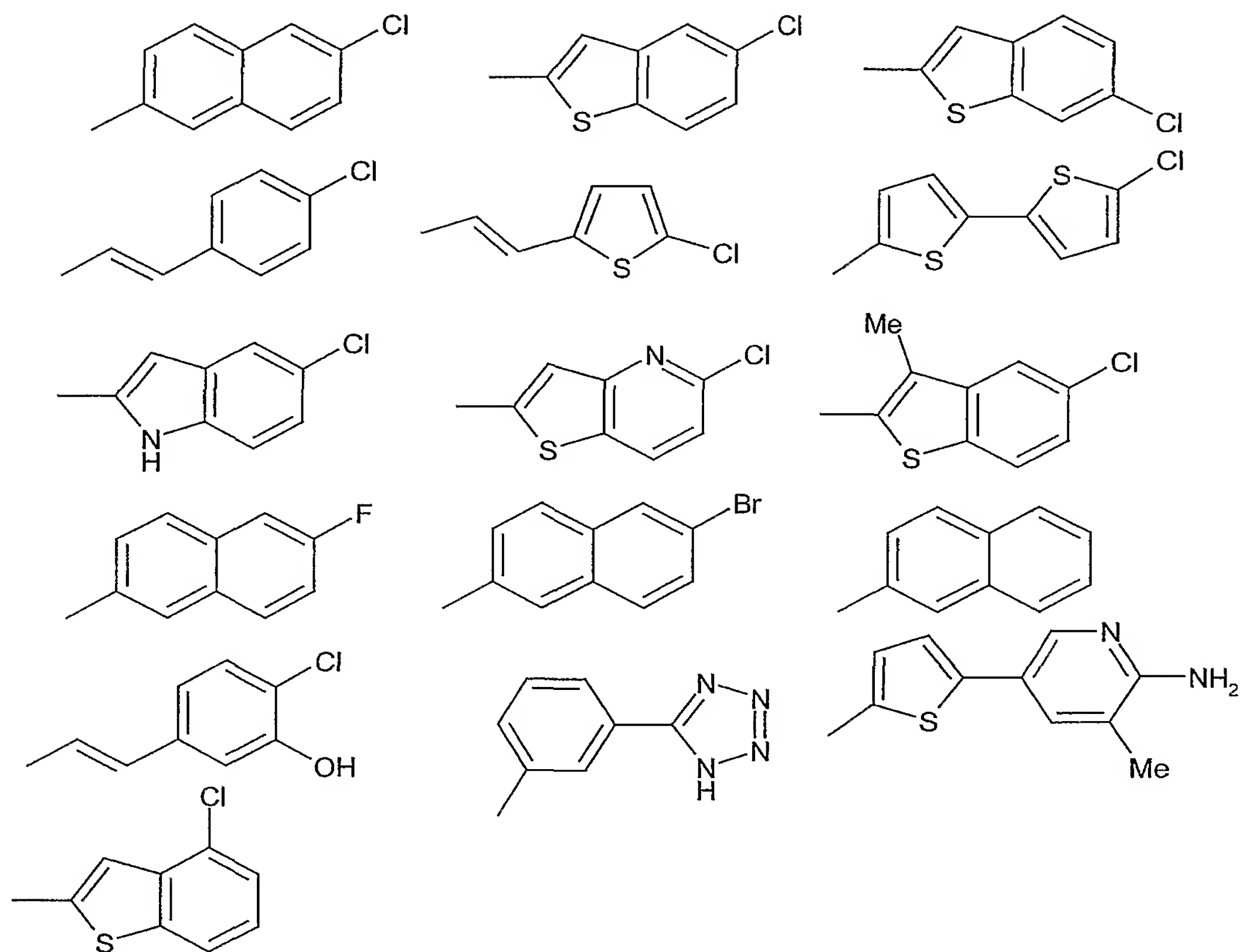
R^1 represents hydrogen, $\text{-C}_{1-6}\text{alkyl}$, $\text{-C}_{3-6}\text{alkenyl}$, $\text{-C}_{2-3}\text{alkylINR}^b\text{R}^a$, $\text{-C}_{2-3}\text{alkylNHCOR}^a$, phenyl
35 or a 5- or 6- membered aromatic heterocycle, or R^1 represents a group X-W wherein X represents $\text{-C}_{1-3}\text{alkylene-}$ and W represents -CN , $\text{-CO}_2\text{H}$, $\text{-CONR}^b\text{R}^c$, $\text{-COC}_{1-6}\text{alkyl}$, $\text{-CO}_2\text{C}_{1-6}\text{alkyl}$ or a 5- or 6- membered aromatic or non-aromatic heterocyclic group containing at least one heteroatom selected from O, N or S.

R^2 and R^3 independently represent hydrogen, or $\text{-C}_{1-3}\text{alkyl}$, with the proviso that one of R^2

40 and R^3 is $\text{-C}_{1-3}\text{alkyl}$ and the other is hydrogen;

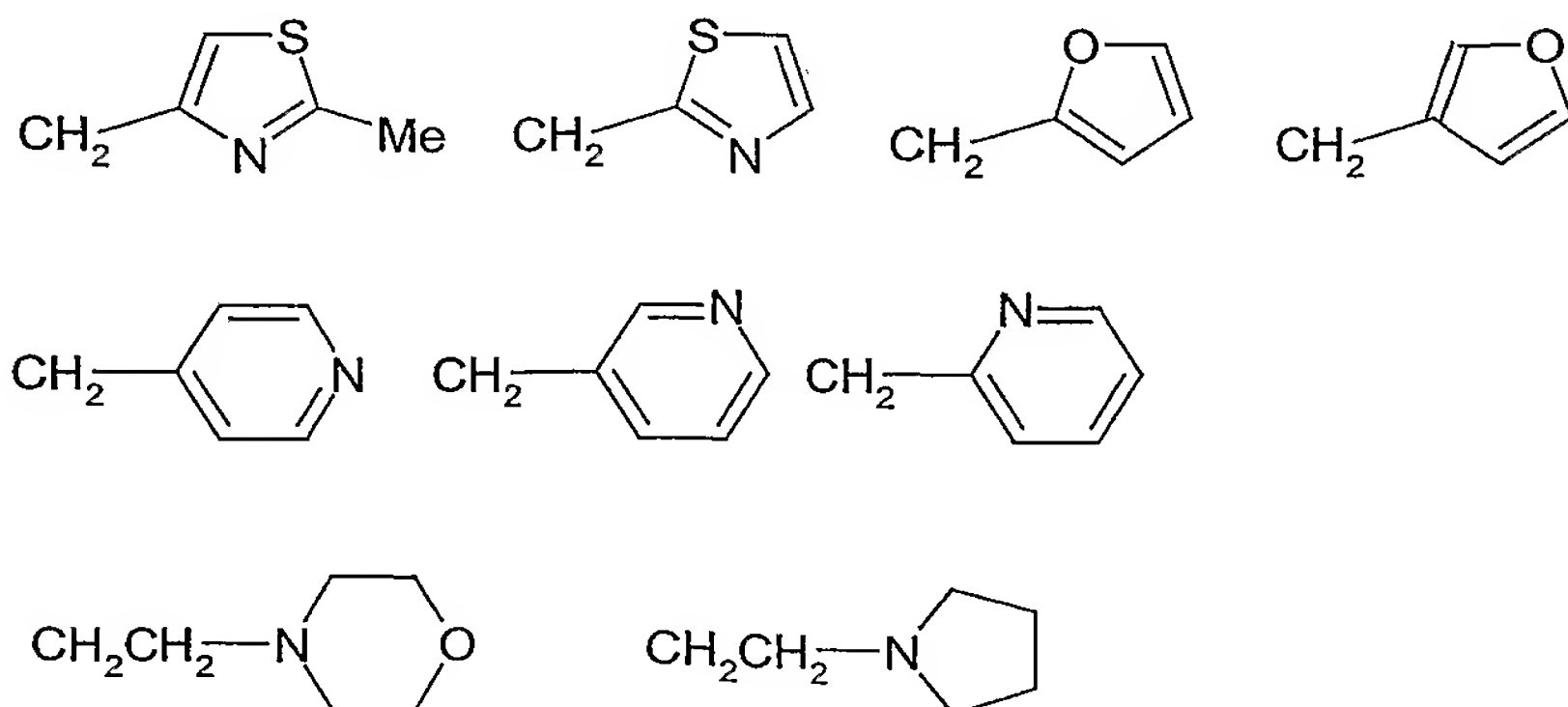
- R⁴ and R⁵, together with the N atom to which they are bonded, form a 4-, 5-, 6-, 7- or 8-membered non-aromatic heterocyclic ring, selected from: piperidine; pyrrolidine; hexamethyleneimine (homopiperidine); morpholine; thiomorpholine; diazepine; tetrahydro-1,6-naphthyridine; 2-azabicyclo[2.2.1]heptane; 2-oxa-5-azabicyclo[2.2.1]heptane; 3,7-diazabicyclo[3.3.1]nonane; 9-oxa-3,7-diazabicyclo[3.3.1]nonane; 2-azabicyclo[2.2.2]octane; 4,6,7,8-tetrahydro-5h-thieno[3,2-c]azepine; 1,2,5,6-tetrahydropyridine; azetidine; 2,5-dihydro-1h-pyrrole; piperazine; hexahydropyrimidine; tetrahydroquinoline; decahydroquinoline; tetrahydroquinoxaline; dihydroisoindole; tetrahydroisoquinoline; tetrahydro-5h-imidazo[4,5-c]pyridine; 1,3,4,5-tetrahydro-2h-2-benzazepine; 2,5-diazabicyclo[2.2.1]heptane; optionally substituted by:
- (i) one or more substituents selected from: -NH₂, -CF₃, F, -OH, =O, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₁₋₆alkylOH, -(C₁₋₃alkyl)NR^bR^c, -(C₀₋₃alkyl)CONR^bR^c, -NHSO₂CF₃, -NHCH₂COCH₂O(C₁₋₃alkyl), -(C₀₋₃alkyl)CO₂C₁₋₄alkyl, -CONHC₂₋₃alkylOH, -COCH₂NR^bR^c, -COCH₂N⁺(CH₃)₃, -CH₂OC₁₋₃alkyl and -CH₂SO₂C₁₋₃alkyl;
- (ii) a group -NHCOR^d or -NR^bR^d,
 R^d represents -C₁₋₆alkyl, -C₂₋₆alkynyl, -C₁₋₆alkylOH, -C₁₋₃alkylCO₂H, -C₁₋₃alkylNR^bR^c, -C₁₋₃alkylCO₂C₁₋₃alkyl, -C₁₋₃alkylOC₁₋₃alkyl and -C₁₋₃alkylCONR^bR^c;
- (iii) a group -Y-R^e,
 Y represents -C₁₋₃alkylene-, -NHCO-, -NHC₁₋₃alkylene-, -NHCO₂C₁₋₃alkylene-, -C₁₋₃alkylNHCO-, -C₁₋₃alkylNHSO₂-, -CO- or a direct link,
 R^e represents phenyl, pyridine, pyrrole, isoxazole, pyrazole, pyrrolidine, cyclopentyl, triazole, pyrazine, furan, thiazole, imidazole, morpholine, piperazine, pyrimidine, piperidine, each of which is optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, halogen, -NH₂;
- with the proviso that where the substituent on the non-aromatic ring formed by R⁴ and R⁵ is -NH₂, -OH, -C₁₋₆alkoxy, -NHSO₂CF₃, -NHCOR^d, -NR^bR^d, -NHCOR^e, or -NHC₁₋₃alkyleneR^e, -NHCO₂C₁₋₃alkyleneR^e, -NHCH₂COCH₂O(C₁₋₃alkyl), the substituent is not attached to a ring carbon atom adjacent to a heteroatom;
- R^a represents hydrogen, -C₁₋₃alkyl, phenyl or a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;
- R^b and R^c independently represent hydrogen or -C₁₋₃alkyl;
- R⁶ represents a substituent selected from:

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and pharmaceutically acceptable salts or solvates thereof.

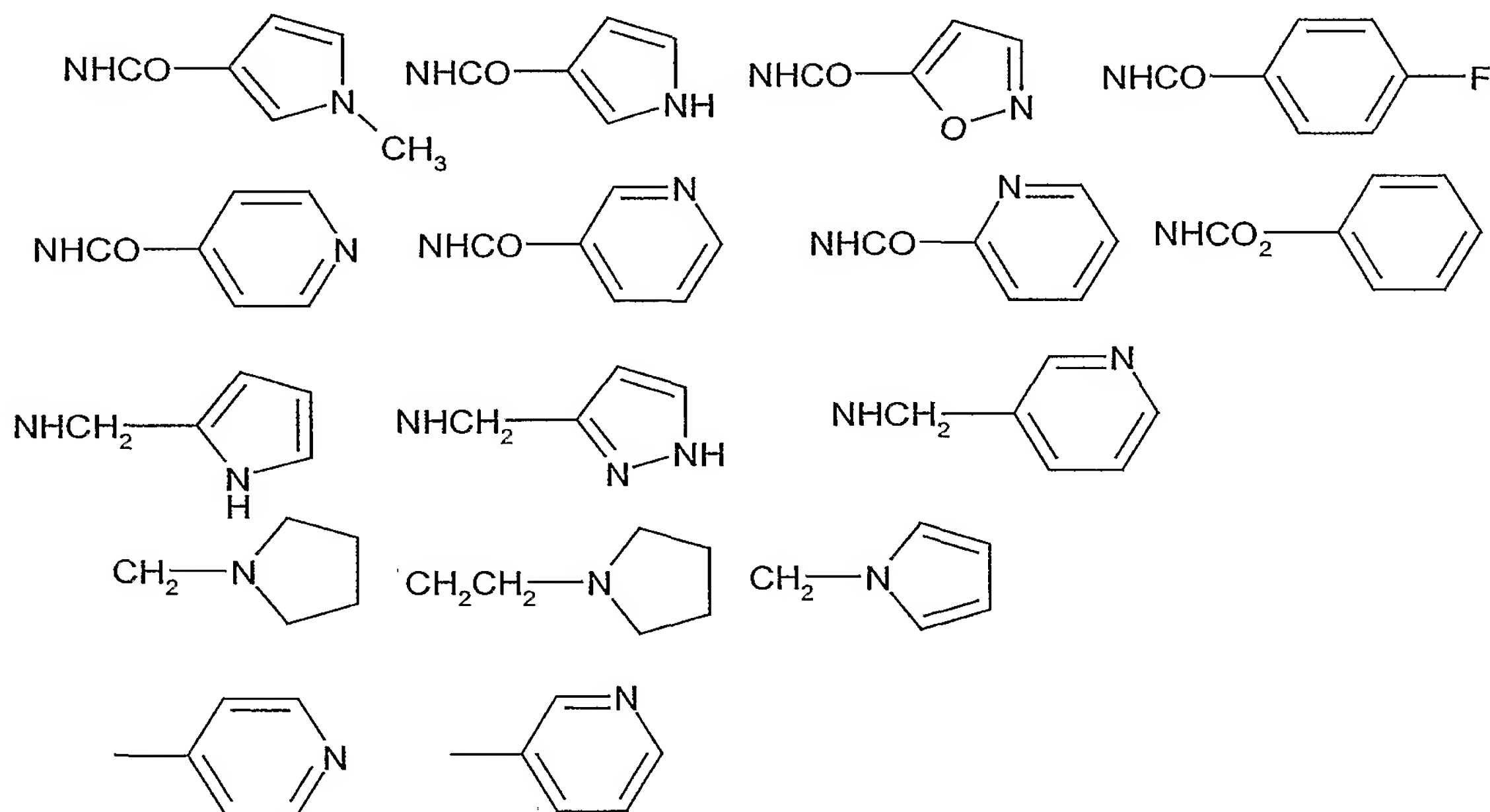
- 5 In an even more preferred aspect the invention provides compounds of formula (I) wherein: R^1 represents a group selected from: hydrogen, $-C_{1-6}$ alkyl, $-\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{NHCOCH}_3$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2t\text{-Butyl}$, $-\text{CH}_2\text{CONH}_2$, $-\text{CH}_2\text{COCH}_2\text{CH}_3$, $-\text{CH}_2\text{Cot-Butyl}$,



R^2 and R^3 independently represent hydrogen, or $-C_{1-3}$ alkyl, with the proviso that one of R^2 and R^3 is $-C_{1-3}$ alkyl and the other is hydrogen;

R^4 and R^5 , together with the N atom to which they are bonded, form a 5-, 6-, 7-, 8-membered non-aromatic heterocyclic ring, selected from: piperidine; pyrrolidine;

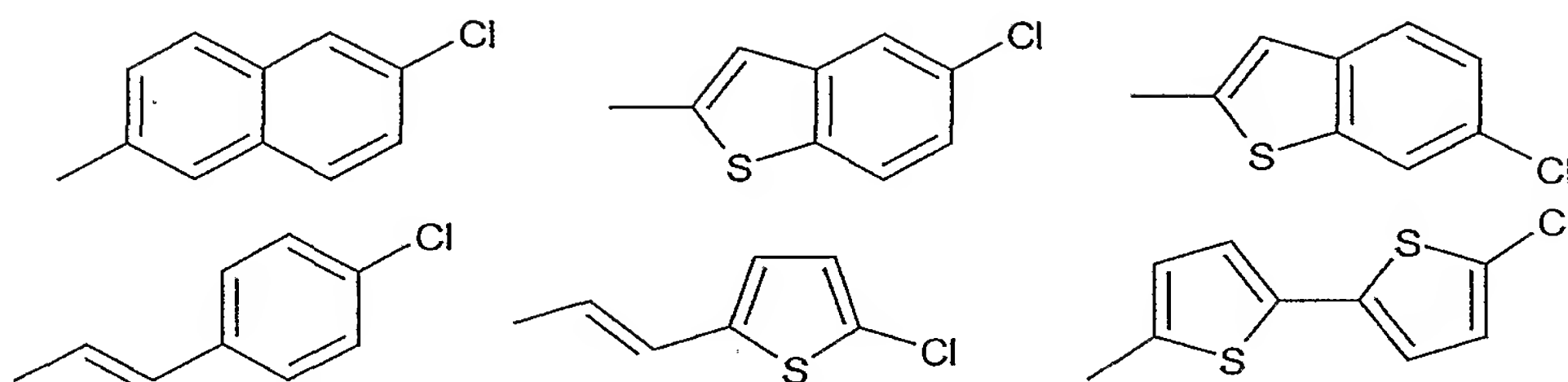
- 5 hexamethyleneimine (homopiperidine); morpholine; thiomorpholine; diazepine; tetrahydro-1,6-naphthyridine; 2-azabicyclo[2.2.1]heptane; 2-oxa-5-azabicyclo[2.2.1]heptane; 3,7-diazabicyclo[3.3.1]nonane; 9-oxa-3,7-diazabicyclo[3.3.1]nonane; 2-azabicyclo[2.2.2]octane; optionally substituted by a substituent selected from: $-CH_3$, $=O$, $-NH_2$, F , $-CH_2OH$, $-CH_2CH_2NHCH_3$, $-NHCOC_{1-3}alkyl$, $-NHCOC\equiv CH$, $-NHCCH_2CH_2CO_2H$; $-NHCCH_2N(CH_3)_2$, $-NHCOC_{1-3}alkylCO_2CH_3$,
- 10



with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is $-NH_2$, $NHCO_2C_{1-3}alkyleneR^e$, $-NHCO-$ or $-NHCH_2-$ the substituent is not attached to a ring carbon atom adjacent to a heteroatom;

- 15 R^a represents hydrogen, $-C_{1-3}alkyl$, phenyl or a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or heterocyclic group being optionally substituted by one or more substituents selected from: $-C_{1-3}alkyl$, $-C_{1-3}alkoxy$, $-C_{1-3}alkylOH$, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;
- R^b and R^c independently represent hydrogen or $-C_{1-3}alkyl$;
- 20 R^d represent a substituent selected from:

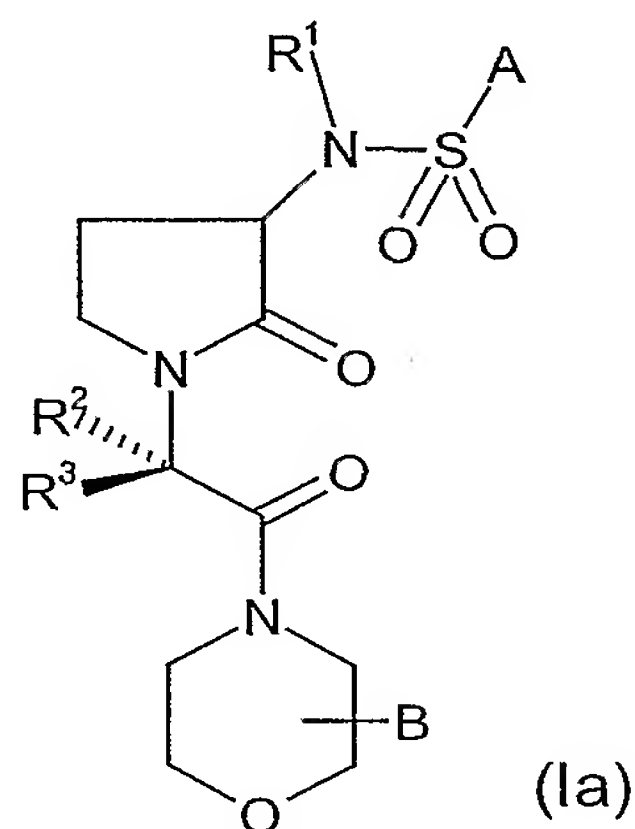
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and pharmaceutically acceptable salts or solvates thereof.

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The present invention also provides compounds of formula (Ia):



wherein:

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R^1 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl or a group X-W, wherein X represents $-C_{1-3}$ alkylene- and W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl, phenyl or 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-C_{1-3}$ alkylOH, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

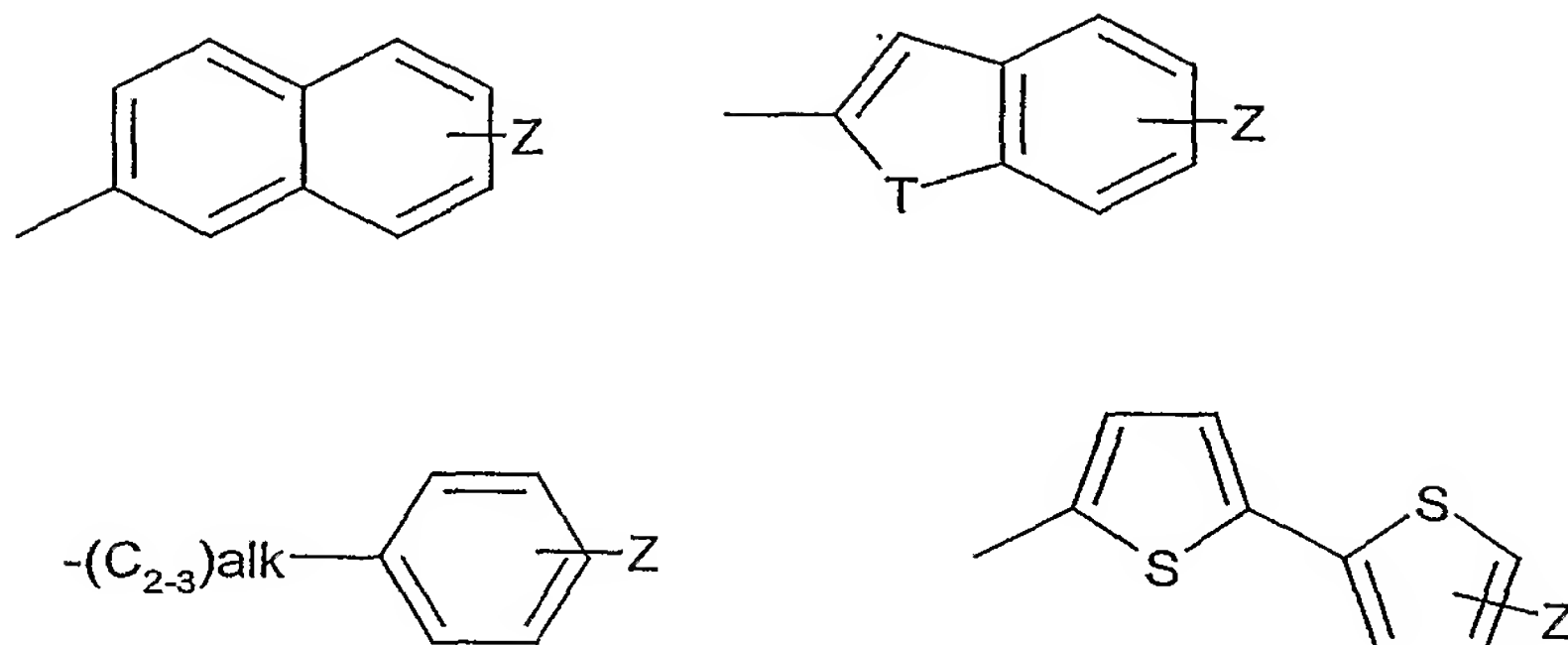
20

R^2 and R^3 independently represent hydrogen, $-C_{1-3}$ alkyl or CF_3 with the proviso that when one of R^2 and R^3 is $-C_{1-3}$ alkyl or CF_3 , the other is hydrogen;

R^b and R^c independently represent hydrogen or $-C_{1-3}$ alkyl;

A represents a group selected from:

20



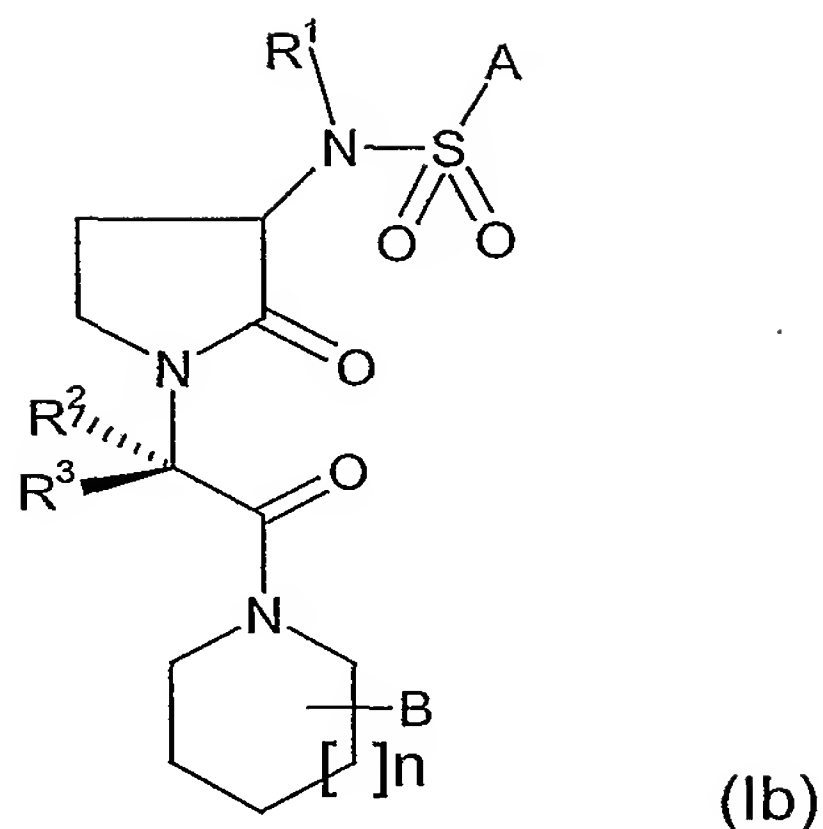
Z represents an optional substituent halogen,
 alk represents alkylene or alkenylene,
 T represents a heteroatom selected from S or N;

- 5 B represents one or more optional substituents on ring carbon atoms selected from: (i) one or more substituents selected from $-\text{CF}_3$, $-\text{F}$, $=\text{O}$, $-\text{CO}_2\text{H}$, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{alkylOH}$, $-(\text{C}_{1-3}\text{alkyl})\text{NR}^b\text{R}^c$, $-(\text{C}_{0-3}\text{alkyl})\text{CONR}^b\text{R}^c$ and $-(\text{C}_{0-3}\text{alkyl})\text{CO}_2\text{C}_{1-3}\text{alkyl}$;
 (ii) a group $-\text{Y}-\text{R}^e$,
 Y represents $-\text{C}_{1-3}\text{alkylene}-$, $-\text{CO}-$, $-\text{C}_{1-3}\text{alkylNH}-$, $-\text{C}_{1-3}\text{alkylNHCO}-$, $-\text{C}_{1-3}\text{alkylNHSO}_2-$, $-\text{CH}_2\text{NHSO}_2\text{CH}_2-$ or a direct link,
 10 R^e represents phenyl, a 5- or 6- membered cycloalkyl or a 5- or 6- membered heterocycle containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by one or more substituents selected from: $-\text{C}_{1-3}\text{alkyl}$, $-\text{C}_{1-3}\text{alkoxy}$, $-\text{C}_{1-3}\text{alkylOH}$, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{NH}_2$, $-\text{CO}_2\text{H}$ and $-\text{OH}$; or
 15 (iii) a second ring R^f which is fused to the heterocyclic ring, wherein R^f represents phenyl, a 5- or 6- membered cycloalkyl group or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, and the fused bicyclic group is optionally substituted by one or more substituents selected from: $-\text{C}_{1-3}\text{alkyl}$, $-\text{C}_{1-3}\text{alkoxy}$, $-\text{C}_{1-3}\text{alkylOH}$, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{NH}_2$, $-\text{CO}_2\text{H}$ and $-\text{OH}$;
 20 and pharmaceutically acceptable salts and solvates thereof.

The present invention also provides compounds of formula (Ib):

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wherein:

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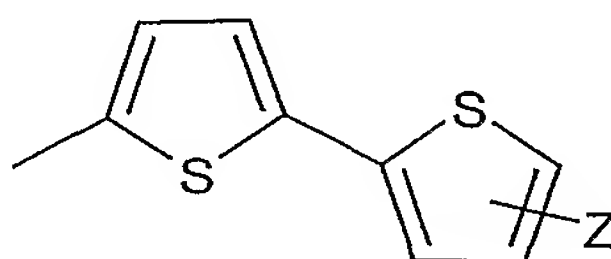
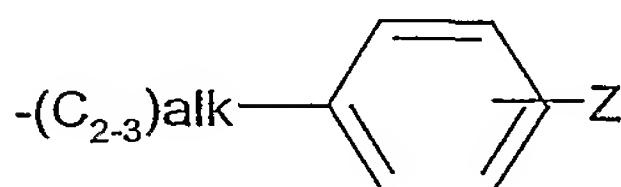
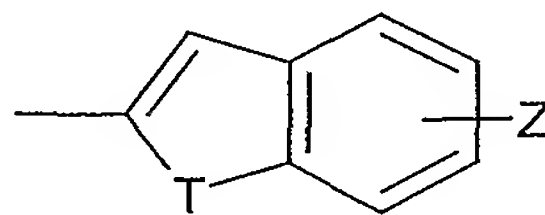
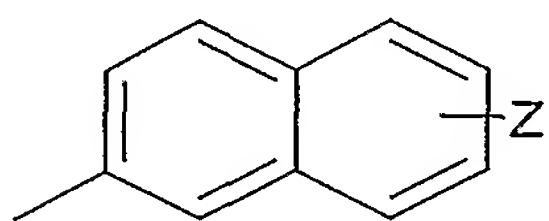
R^1 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl or a group X-W, wherein X represents $-C_{1-3}$ alkylene- and W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl, phenyl or 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-C_{1-3}$ alkylOH, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

10

R^2 and R^3 independently represent hydrogen, $-C_{1-3}$ alkyl or CF_3 with the proviso that when one of R^2 and R^3 is $-C_{1-3}$ alkyl or CF_3 , the other is hydrogen;

15

R^b and R^c independently represent hydrogen or $-C_{1-3}$ alkyl;



A represents a group selected from:

Z represents an optional substituent halogen,

alk represents alkylene or alkenylene,

T represents a heteroatom selected from S or N;

n represents 0 or 1;

5

B represents one or more optional substituents on ring carbon atoms selected from:

(i) one or more substituents selected from: $-NH_2$, $-CF_3$, F, $-OH$, $=O$, $-CO_2H$, $-C_{1-6}alkyl$, $-C_{1-6}alkoxy$, $-C_{1-6}alkylOH$, $-(C_{1-3}alkyl)NR^bR^c$, $-(C_{0-3}alkyl)CONR^bR^c$, $-NHSO_2CF_3$, $-NHSO_2(C_{0-3}alkyl)R^a$ and $-(C_{0-3}alkyl)CO_2C_{1-3}alkyl$;

10 R^a represents hydrogen, $-C_{1-3}alkyl$, phenyl or a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or heterocyclic group being optionally substituted by one or more substituents selected from: $-C_{1-3}alkyl$, $-C_{1-3}alkoxy$, $-C_{1-3}alkylOH$, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

(ii) a group $-NHCOR^d$ or $-NR^bR^d$;

15 R^d represents $-C_{1-6}alkyl$, $-C_{2-6}alkynyl$, $-C_{1-6}alkoxy$, $-C_{1-6}alkylOH$, $-C_{1-3}alkylCO_2H$, $-C_{1-3}alkylNR^bR^c$, $-C_{1-3}alkylCO_2C_{1-3}alkyl$ or $-C_{1-3}alkylCONR^bR^c$;

(iii) a group $-Y-R^e$,

Y represents $-C_{1-3}alkylene-$, $-NHCO-$, $-NHCO_2C_{1-3}alkylene-$, $-NHC_{1-3}alkylene-$, $-CO-$, $-C_{1-3}alkylNH-$, $-C_{1-3}alkylNHCO-$, $-C_{1-3}alkylNHSO_2-$, $-CH_2NHSO_2CH_2-$ or a direct link,

20 R^e represents phenyl, a 5- or 6- membered cycloalkyl or a 5- or 6- membered heterocycle containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by one or more substituents selected from: $-C_{1-3}alkyl$, $-C_{1-3}alkoxy$, $-C_{1-3}alkylOH$, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$; or

(iv) a second ring R^f which is fused to the heterocyclic ring, wherein R^f represents phenyl, a

25 5- or 6- membered cycloalkyl group or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, and the fused bicyclic group is optionally substituted by one or more substituents selected from: $-C_{1-3}alkyl$, $-C_{1-3}alkoxy$, $-C_{1-3}alkylOH$, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

with the proviso that where B is $-NH_2$, $-OH$, $-C_{1-6}alkoxy$, $-NHSO_2CF_3$, $-NHSO_2(C_{0-3}alkyl)R^a$, $-$

30 $NHCOR^d$, $-NR^bR^d$, $-NHCOR^e$, $-NHCO_2C_{1-3}alkyleneR^e$ or $-NHC_{1-3}alkyleneR^e$, it is not attached to a ring carbon atom adjacent to a heteroatom;

and pharmaceutically acceptable derivatives thereof.

The present invention also provides compounds of formula (I) wherein:

35 R^1 represents hydrogen, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-C_{2-3}alkylOH$, $-C_{2-3}alkylNR^bR^a$, $-C_{2-3}alkylNHCOR^a$, $-C_{2-3}alkylNHCO_2R^b$, $-C_{2-3}alkylNHSO_2R^b$, $-C_{2-3}alkylNHCONR^bR^c$ or a group X-W;

X represents $-C_{1-3}alkylene-$, propenylene, propynylene;

W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}alkyl$, $-CO_2C_{1-6}alkyl$, $-CO_2C_{2-6}alkenyl$, $-$

40 ONR^bR^c , $-OC_{1-6}alkyl$, $-OCH_2phenyl$, phenyl or 5- or 6- membered aromatic heterocyclic

group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;

R² and R³ independently represent hydrogen or -C₁₋₃alkyl, with the proviso that when one of

5 R² and R³ is -C₁₋₃alkyl, the other is hydrogen;

R⁴ and R⁵, together with the N atom to which they are bonded, form a 5- or 6- membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom, and optionally substituted by:

(i) one or more substituents selected from -NH₂, -CF₃, -OH, -CO₂H, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₁₋₆alkylOH, -(C₁₋₃alkyl)NR^bR^c, -(C₀₋₃alkyl)CONR^bR^c and NHSO₂CF₃;

(ii) a group -NHCOR^d or -NR^bR^d,

R^d represents -C₁₋₆alkyl, -C₂₋₆alkynyl, -C₁₋₆alkylOH, -C₁₋₃alkylCO₂H, -C₁₋₃alkylNR^bR^c, -C₁₋₃alkylCO₂CH₃ or -C₁₋₃alkylCONR^bR^c;

(iii) a group -Y-R^e,

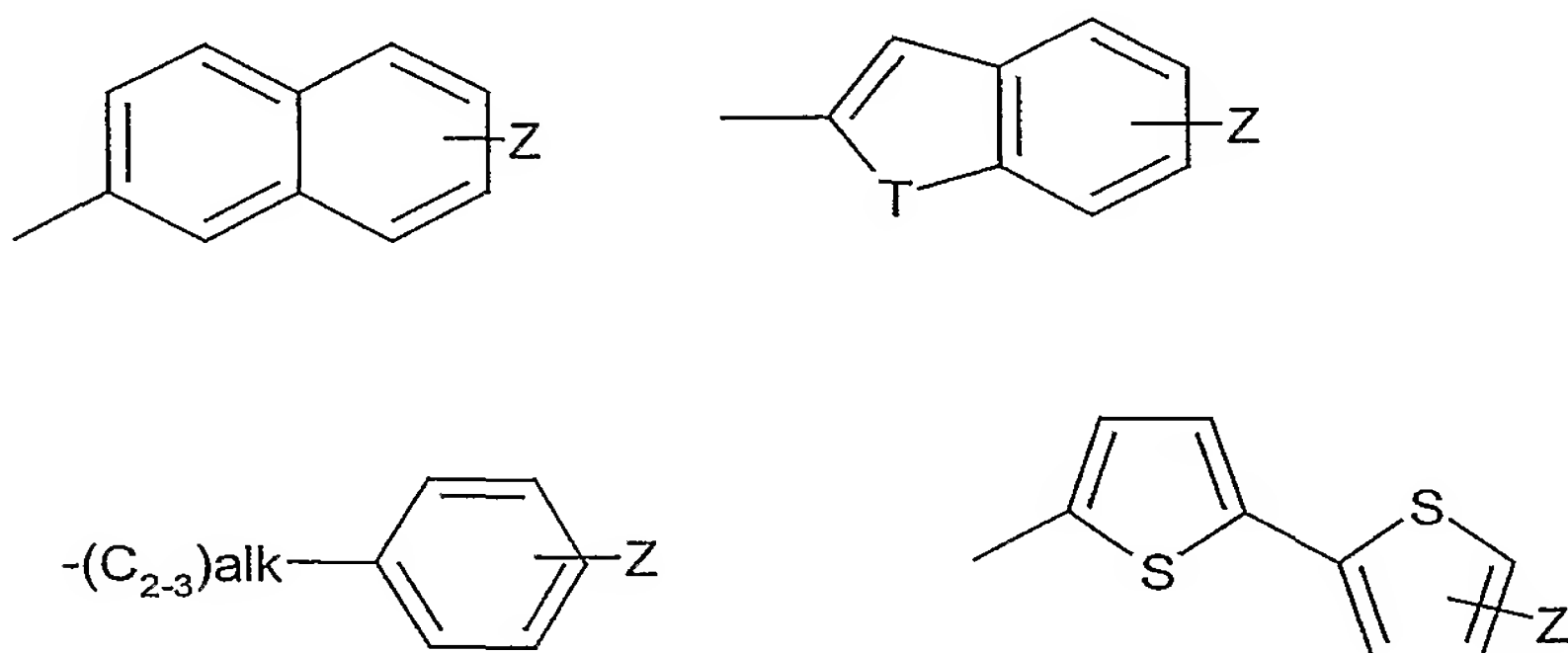
15 Y represents -C₁₋₃alkylene-, -NHCO-, -NHCO₂C₁₋₃alkylene-, -NHC₁₋₃alkylene- or -C₁₋₃alkylNHSO₂-,

R^e represents imidazole, pyrrole, pyrazole, pyridine, pyrimidine, furan, oxazole, 1,2,4-triazole, phenyl or pyrrolidine optionally substituted by -C₁₋₃alkyl, NH₂ or -C₁₋₃alkylOH;

with the proviso that where the substituent on the non-aromatic ring formed by R⁴ and R⁵ is -NH₂, -OH, -C₁₋₆alkoxy, -NHSO₂CF₃, -NHCOR^d, -NR^bR^d, -NHCOR^e, -NHCO₂C₁₋₃alkyleneR^e or -NHC₁₋₃alkyleneR^e, the substituent is not attached to a ring carbon atom adjacent to a heteroatom;

20 R^b and R^c independently represent hydrogen or -C₁₋₃alkyl;

R⁶ represents a group selected from:



25 Z represents an optional substituent halogen,

alk represents alkylene or alkenylene,

T represents a heteroatom selected from S or N;

30 The present invention also provides compounds of formula (I) wherein:

R^1 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl or a group X-W wherein X represents $-C_{1-3}$ alkylene- and W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S;

5 R^2 and R^3 independently represent hydrogen or $-C_{1-3}$ alkyl, with the proviso that when one of R^2 and R^3 is $-C_{1-3}$ alkyl, the other is hydrogen;

R^4 and R^5 , together with the N atom to which they are bonded, form a 5- or 6- membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom, and optionally substituted by:

(i) 10 one or more substituents selected from $-NH_2$, $-CF_3$, $-OH$, $-CO_2H$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-C_{1-6}$ alkylOH, $-(C_{1-3}alkyl)NR^bR^c$, $-(C_{0-3}alkyl)CONR^bR^c$ and $-NHSO_2CF_3$;

(ii) a group $-NHCOR^d$ or $-NR^bR^d$,

R^d represents $-C_{1-6}$ alkyl, $-C_{2-6}$ alkynyl, $-C_{1-6}$ alkylOH, $-C_{1-6}$ alkylCO₂H, $-C_{1-3}alkylNR^bR^c$, $-C_{1-3}alkylCO_2CH_3$ or $-C_{1-3}alkylCONR^bR^c$,

15 (iii) a group $-Y-R^e$,

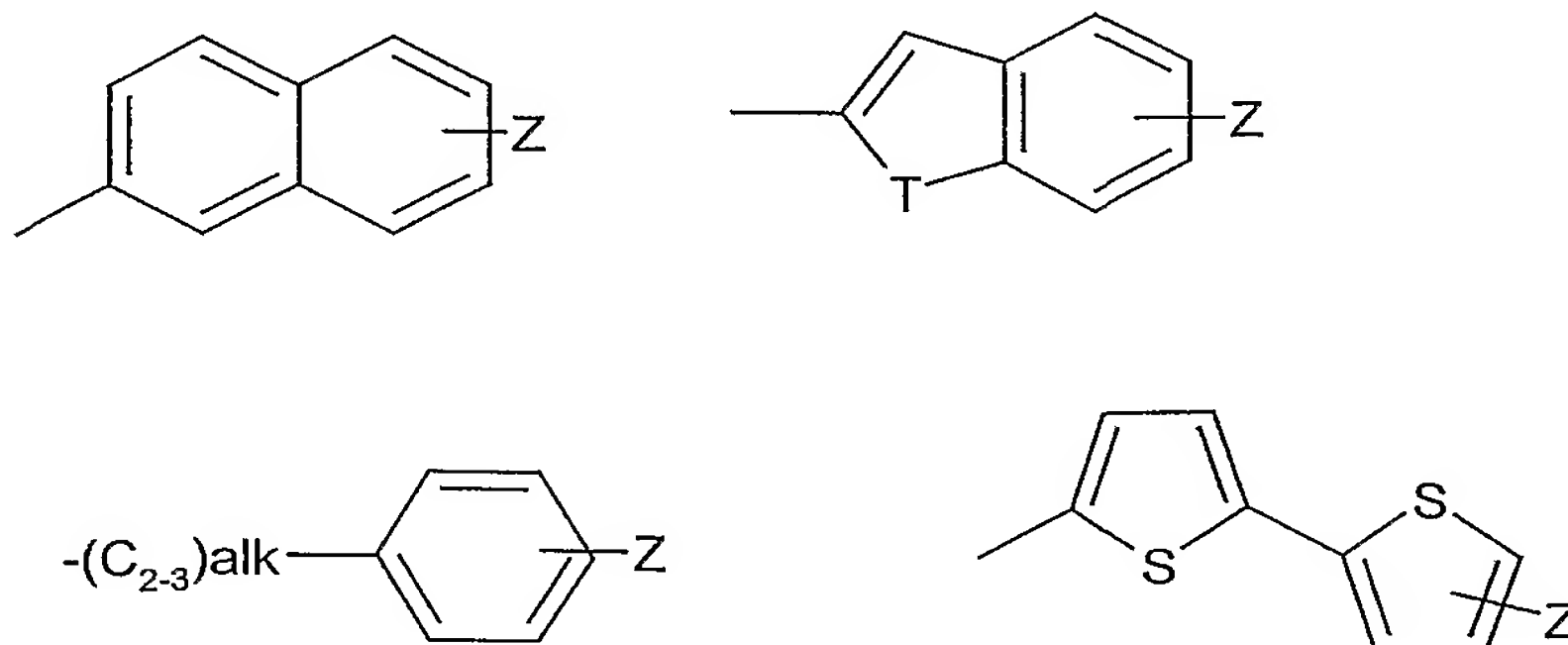
Y represents $-C_{1-3}alkylene-$, $-NHCO-$, $-NHCO_2C_{1-3}alkylene-$ or $-NHC_{1-3}alkylene-$, $-C_{1-3}alkylNHSO_2-$,

R^e represents imidazole, pyrrole, pyrazole, pyridine, pyrimidine, furan, oxazole, 1,2,4-triazole, phenyl or pyrrolidine optionally substituted by $-C_{1-3}alkyl$, NH_2 or $-C_{1-3}alkylOH$;

20 with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is $-NH_2$, $-OH$, $-C_{1-6}alkoxy$, $-NHSO_2CF_3$, $-NHCOR^d$, $-NR^bR^d$, $-NHCOR^e$, $-NHCO_2C_{1-3}alkyleneR^e$ or $-NHC_{1-3}alkyleneR^e$, the substituent is not attached to a ring carbon atom adjacent to a heteroatom;

R^b and R^c independently represent hydrogen or $-C_{1-3}alkyl$;

25 R^6 represents a group selected from:



Z represents an optional substituent halogen,

alk represents alkylene or alkenylene,

T represents a heteroatom selected from S or N;

30

The present invention also provides compounds of formula (I) wherein:

R^1 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{2-3}$ alkylOH, $-C_{2-3}$ alkylNR^bR^a, $-C_{2-3}$ alkylNHCOR^a, $-C_{2-3}$ alkylNHCO₂R^b, $-C_{2-3}$ alkylNH₂SO₂R^b, $-C_{2-3}$ alkylNHCONR^bR^c or a group X-W;

X represents $-C_{1-3}$ alkylene-, propenylene, propynylene;

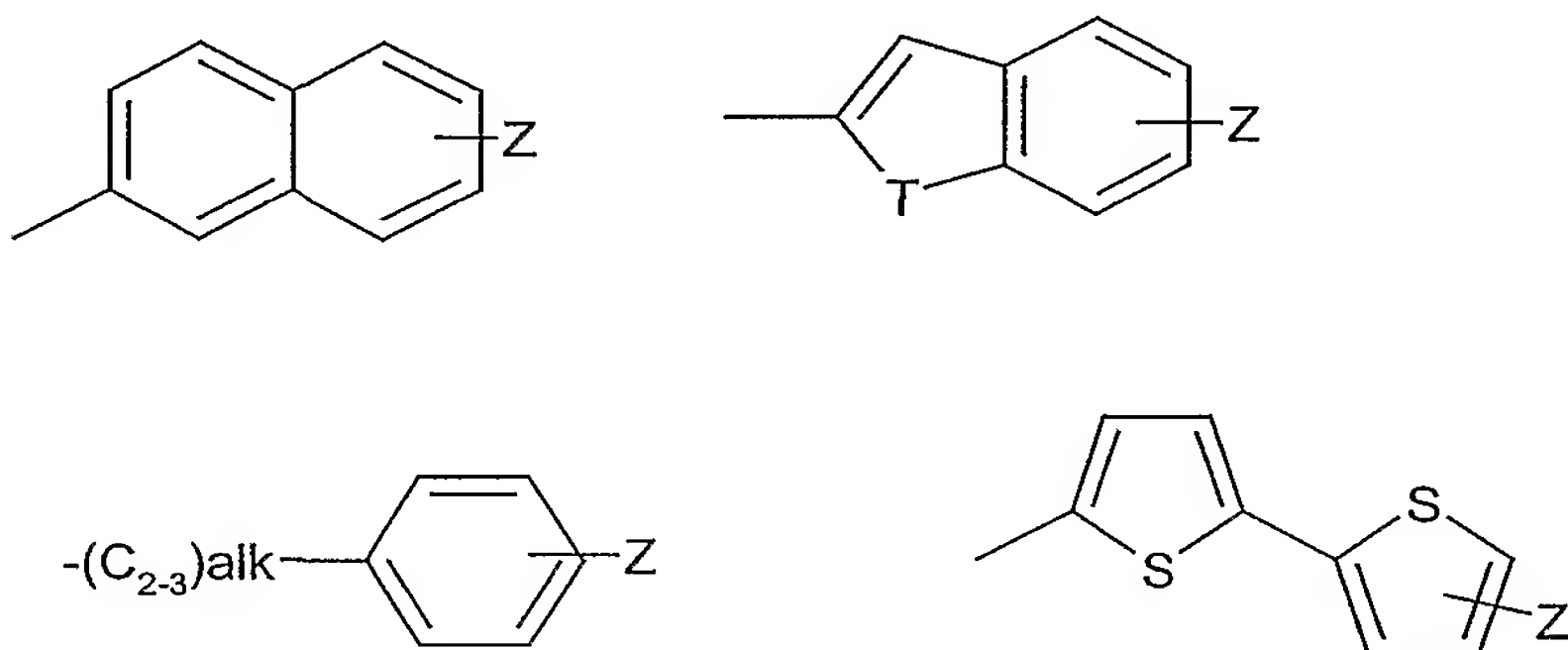
5 W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl, $-CO_2C_{2-6}$ alkenyl, $-OCONR^bR^c$, $-OC_{1-6}$ alkyl, $-OCH_2$ phenyl, phenyl or 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-C_{1-3}$ alkylOH, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

10 R^2 and R^3 independently represent hydrogen or $-C_{1-3}$ alkyl, with the proviso that when one of R^2 and R^3 is $-C_{1-3}$ alkyl, the other is hydrogen;

R^4 and R^5 , together with the N atom to which they are bonded, represent piperidine, 2-(pyrrolidin-1-ylmethyl)pyrrolidine or morpholine;

R^b and R^c independently represent hydrogen or $-C_{1-3}$ alkyl;

15 R^6 represents a group selected from:



Z represents an optional substituent halogen,

alk represents alkylene or alkenylene,

T represents a heteroatom selected from S or N;

20

The present invention also provides compounds of formula (I) wherein:

R^1 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{2-3}$ alkylOH, $-C_{2-3}$ alkylNR^bR^a, $-C_{2-3}$ alkylNHCOR^a, $-C_{2-3}$ alkylNHCO₂R^b, $-C_{2-3}$ alkylNH₂SO₂R^b, $-C_{2-3}$ alkylNHCONR^bR^c or a group X-W;

25 X represents $-C_{1-3}$ alkylene-, propenylene, propynylene;

W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl, $-CO_2C_{2-6}$ alkenyl, $-OCONR^bR^c$, $-OC_{1-6}$ alkyl, $-OCH_2$ phenyl, phenyl or 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-C_{1-3}$ alkylOH, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

30 C_{1-3} alkyl, $-C_{1-3}$ alkoxy, $-C_{1-3}$ alkylOH, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

R^2 and R^3 independently represent hydrogen or $-C_{1-3}$ alkyl, with the proviso that when one of R^2 and R^3 is $-C_{1-3}$ alkyl, the other is hydrogen;

R^4 and R^5 , together with the N atom to which they are bonded, form a 5- or 6- membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom, and optionally

5 substituted by:

(i) one or more substituents selected from $-NH_2$, $-CF_3$, $-OH$, $-CO_2H$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-C_{1-6}$ alkylOH, $-(C_{1-3}alkyl)NR^bR^c$, $-(C_{0-3}alkyl)CONR^bR^c$ or $-NHSO_2CF_3$;

(ii) a group $-NHCOR^d$ or $-NR^bR^d$,

10 R^d represents $-C_{1-6}$ alkyl, $-C_{2-6}$ alkynyl, $-C_{1-6}$ alkylOH, $-C_{1-6}$ alkylCO₂H, $-C_{1-3}alkylNR^bR^c$, $-C_{1-3}alkylCO_2CH_3$ or $-C_{1-3}alkylCONR^bR^c$,

(iii) a group $-Y-R^e$,

Y represents $-C_{1-3}alkylene-$, $-NHCO-$, $-NHCO_2C_{1-3}alkylene-$, $-NHC_{1-3}alkylene-$ or $-C_{1-3}alkylNHSO_2-$,

15 R^e represents imidazole, pyrrole, pyrazole, pyridine, pyrimidine, furan, oxazole, 1,2,4-triazole, phenyl or pyrrolidine optionally substituted by $-C_{1-3}alkyl$, NH_2 or $-C_{1-3}alkylOH$;

with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is $-NH_2$, $-OH$, $-C_{1-6}alkoxy$, $-NHSO_2CF_3$, $-NHCOR^d$, $-NR^bR^d$, $-NHCOR^e$, $-NHCO_2C_{1-3}alkyleneR^e$ or $-NHC_{1-3}alkyleneR^e$, the substituent is not attached to a ring carbon atom adjacent to a heteroatom;

20 R^b and R^c independently represent hydrogen or $-C_{1-3}alkyl$;

R^6 represents 6-chloronaphthyl, 5'-chloro-2,2'-bithiophene, (4-chlorophenyl)ethene or 6-chloro-1-benzothiophene.

The present invention also provides compounds of formula (I) wherein:

25 R^1 represents hydrogen, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$ or a group X-W wherein X represents $-C_{1-3}alkylene-$ and W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}alkyl$, $-CO_2C_{1-6}alkyl$ or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S;

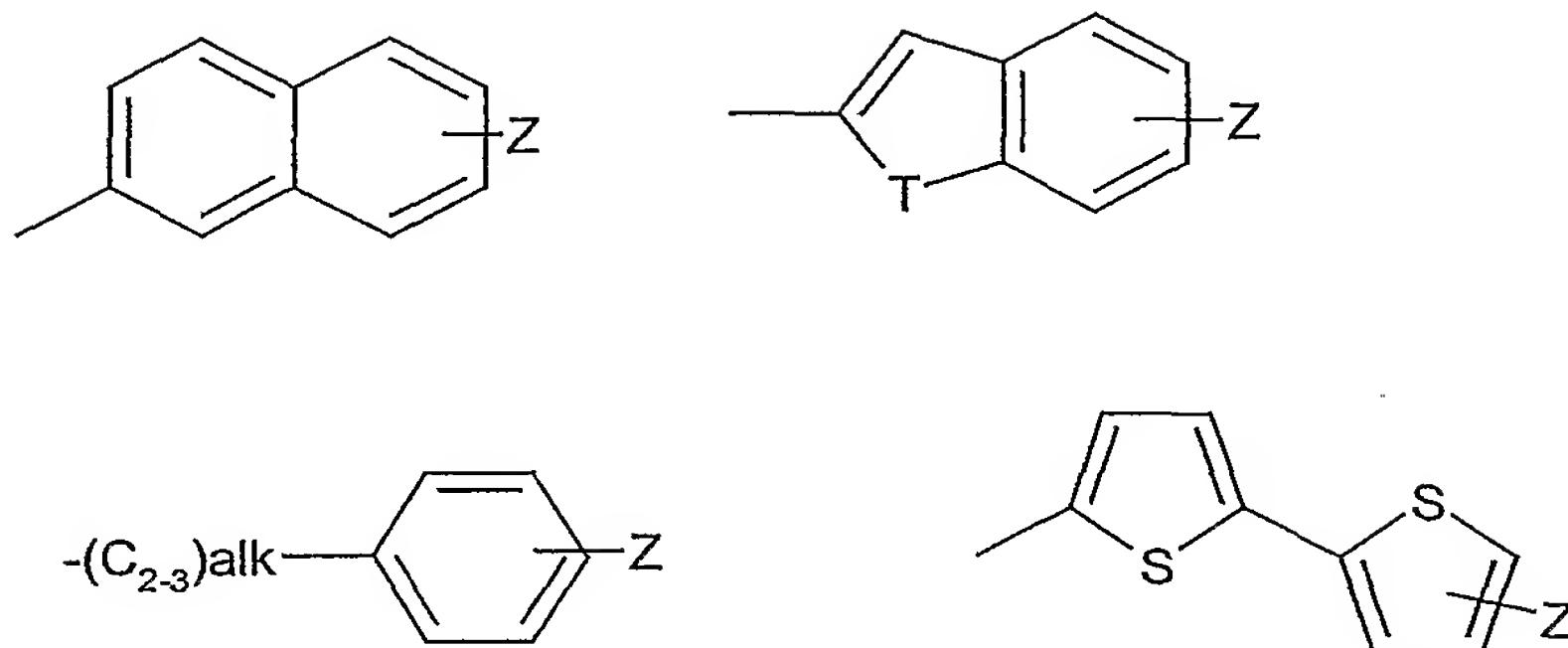
R^2 and R^3 independently represent hydrogen or $-C_{1-3}alkyl$, with the proviso that when one of

30 R^2 and R^3 is $-C_{1-3}alkyl$, the other is hydrogen;

R^4 and R^5 , together with the N atom to which they are bonded, represent piperidine, 2-(pyrrolidin-1-ylmethyl)pyrrolidine or morpholine,

R^b and R^c independently represent hydrogen or $-C_{1-3}alkyl$,

R^6 represents a group selected from:



Z represents an optional substituent halogen,

alk represents alkylene or alkenylene,

T represents a heteroatom selected from S or N;

5

The present invention also provides compounds of formula (I) wherein:

R¹ represents hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl or a group X-W wherein X represents -C₁₋₃alkylene- and W represents -CN, -CO₂H, -CONR^bR^c, -COC₁₋₆alkyl, -CO₂C₁₋₆alkyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from

10 O, N or S;

R² and R³ independently represent hydrogen or -C₁₋₃alkyl, with the proviso that when one of R² and R³ is -C₁₋₃alkyl, the other is hydrogen;

R⁴ and R⁵, together with the N atom to which they are bonded, form a 5- or 6- membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom, and optionally

15 substituted by:

(i) one or more substituents selected from -NH₂, -CF₃, -OH, -CO₂H, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₁₋₆alkylOH, -(C₁₋₃alkyl)NR^bR^c, -(C₀₋₃alkyl)CONR^bR^c and -NHSO₂CF₃;

(ii) a group -NHCOR^d or -NR^bR^d,

R^d represents -C₁₋₆alkyl, -C₂₋₆alkynyl, -C₁₋₆alkylOH, -C₁₋₆alkylCO₂H, -C₁₋₃alkylNR^bR^c, -C₁₋₃alkylCO₂CH₃ or -C₁₋₃alkylCONR^bR^c,

20 (iii) a group -Y-R^e,

Y represents -C₁₋₃alkylene-, -NHCO-, -NHCO₂C₁₋₃alkylene-, -NHC₁₋₃alkylene- or -C₁₋₃alkylNHSO₂-,

R^e represents imidazole, pyrrole, pyrazole, pyridine, pyrimidine, furan, oxazole, 1,2,4-triazole, phenyl or pyrrolidine optionally substituted by -C₁₋₃alkyl, NH₂ or -C₁₋₃alkylOH;

25 with the proviso that where the substituent on the non-aromatic ring formed by R⁴ and R⁵ is -NH₂, -OH, -C₁₋₆alkoxy, -NHSO₂CF₃, -NHCOR^d, -NR^bR^d, -NHCOR^e, -NHCO₂C₁₋₃alkyleneR^e or -NHC₁₋₃alkyleneR^e, the substituent is not attached to a ring carbon atom adjacent to a heteroatom;

30 R^b and R^c independently represent hydrogen or -C₁₋₃alkyl;

R⁶ represents 6-chloronaphthyl, 5'-chloro-2,2'-bithiophene, (4-chlorophenyl)ethene or 6-chloro-1-benzothiophene.

The present invention also provides compounds of formula (I) wherein:

- 5 R¹ represents hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₂₋₃alkylOH, -C₂₋₃alkylNR^bR^a, -C₂₋₃alkylNHCOR^a, -C₂₋₃alkylNHCO₂R^b, -C₂₋₃alkylNH₂SO₂R^b, -C₂₋₃alkylNHCONR^bR^c or a group X-W;
- X represents -C₁₋₃alkylene-, propenylene, propynylene;
- W represents -CN, -CO₂H, -CONR^bR^c, -COC₁₋₆alkyl, -CO₂C₁₋₆alkyl, -CO₂C₂₋₆alkenyl, -
- 10 OCONR^bR^c, -OC₁₋₆alkyl, -OCH₂phenyl, phenyl or 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;
- R² and R³ independently represent hydrogen or -C₁₋₃alkyl, with the proviso that when one of
- 15 R² and R³ is -C₁₋₃alkyl, the other is hydrogen;
- R⁴ and R⁵, together with the N atom to which they are bonded, represent piperidine, 2-(pyrrolidin-1-ylmethyl)pyrrolidine or morpholine;
- R^b and R^c independently represent hydrogen or -C₁₋₃alkyl,
- R⁶ represents 6-chloronaphthyl, 5'-chloro-2,2'-bithiophene, (4-chlorophenyl)ethene or 6-
- 20 chloro-1-benzothiophene.

The present invention also provides compounds of formula (I) wherein:

- R¹ represents hydrogen, -C₁₋₆alkyl, -C₂₋₆alkenyl or a group X-W wherein X represents -C₁₋₃alkylene- and W represents -CN, -CO₂H, -CONR^bR^c, -COC₁₋₆alkyl, -CO₂C₁₋₆alkyl or a 5- or
- 25 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S;
- R² and R³ independently represent hydrogen or -C₁₋₃alkyl, with the proviso that when one of R² and R³ is -C₁₋₃alkyl, the other is hydrogen;
- R⁴ and R⁵, together with the N atom to which they are bonded, represent piperidine, 2-
- 30 (pyrrolidin-1-ylmethyl)pyrrolidine or morpholine,
- R^b and R^c independently represent hydrogen or -C₁₋₃alkyl,
- R⁶ represents 6-chloronaphthyl, 5'-chloro-2,2'-bithiophene, (4-chlorophenyl)ethene or 6-chloro-1-benzothiophene.

- 35 The compounds of formula (I), (Ia), (Ib), (Ic) contain chiral (asymmetric) centres. The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are within the scope of the present invention.

- 40 As used herein, the terms "alkyl" and "alkoxy" mean both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl (-CH₃), ethyl (-

C₂H₅), propyl (-C₃H₇) and butyl (-C₄H₉). Examples of alkoxy groups include methoxy (-OCH₃) and ethoxy (-OC₂H₅).

As used herein, the term "alkylene" means both straight and branched chain saturated hydrocarbon linker groups. Examples of alkylene groups include methylene (-CH₂-) and ethylene (-CH₂CH₂-).

As used herein, the term "alkenyl" means both straight and branched chain unsaturated hydrocarbon groups, wherein the unsaturation is present only as double bonds. Examples of alkenyl groups include ethenyl (-CH=CH₂) and propenyl (-CH=CHCH₃ or -CH₂CH=CH₂).

As used herein, the term "alkenylene" means both straight and branched chain unsaturated hydrocarbon linker groups, wherein the unsaturation is present only as double bonds. Examples of alkenylene groups includes ethenylene (-CH=CH-) and propenylene (-CH₂-CH=CH- or -CH=CH-CH₂-).

As used herein, the term "alkynyl" means both straight and branched chain unsaturated hydrocarbon groups, wherein the unsaturation is present only as triple bonds. Examples of alkynyl groups include propynyl (e.g. -CH₂-C≡CH, -C≡C-CH₃).

As used herein, the term "propynylene" means a straight chain unsaturated hydrocarbon linker group, wherein the unsaturation is present as a triple bond (-CH₂-C≡C-).

As used herein, the term "halogen" means fluorine, chlorine, bromine and iodine.

As used herein, the term "cycloalkyl group" means an aliphatic ring (a saturated carbocyclic group). Examples of cycloalkyl groups include cyclopentyl and cyclohexyl.

As used herein, the term "heterocyclic group" means rings containing one or more heteroatoms selected from: N, S and O. The heterocycle may be aromatic or non-aromatic, i.e., may be saturated, partially or fully unsaturated. Examples of 5-membered groups include thienyl, pyrrolyl, pyrrolidinyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, isoxazolyl and furanyl, 6-membered groups include pyridyl, pyrazyl and pyrimidyl, morpholinyl, thiomorpholinyl, 7-membered groups include azepinyl.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use.

As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester or carbamate, or salt or solvate of such a prodrug, of a compound of formula (I), (Ia), (Ib), or (Ic), which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I), (Ia), (Ib), or (Ic), or an active metabolite or residue thereof. Preferred pharmaceutically acceptable derivatives are salts and solvates.

Suitable salts according to the invention include those formed with both organic and inorganic acids and bases. Pharmaceutically acceptable acid addition salts include those formed from mineral acids such as: hydrochloric, hydrobromic, sulphuric, phosphoric, acid; and organic acids such as: citric, tartaric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, formic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases, including salts of primary, secondary and tertiary amines, such as isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexyl amine and N-methyl-D-glucamine. Particularly preferred pharmaceutically acceptable salts include those formed from hydrochloric, trifluoroacetic and formic acids.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of formula (I), (Ia), (Ib), or (Ic) are within the scope of the invention.

Salts and solvates of compounds of formula (I), (Ia), (Ib), or (Ic) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I), (Ia), (Ib), or (Ic) and their pharmaceutically acceptable salts and solvates.

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable

pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt.

Preferred compounds of the invention include:

- 5 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(5-oxo-1,4-diazepan-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-{2-[(4-methylpiperazin-1-yl)methyl]pyrrolidin-1-yl}-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate;
- 10 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-[2-(morpholin-4-ylmethyl)pyrrolidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 15 6-Chloro-N-[(3S)-1-[(1S)-2-(2,6-dimethylmorpholin-4-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-(3-methylmorpholin-4-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide ;
- 20 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide ;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-{2-[(methylsulfonyl)methyl]morpholin-4-yl}-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 25 6-Chloro-N-[(3S)-1-[(1S)-2-[2-(methoxymethyl)morpholin-4-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 4-[(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]-N-methylmorpholine-2-carboxamide;
- 4-[(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]-N-(2-hydroxypropyl)morpholine-2-carboxamide ;
- 30 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)morpholin-4-yl]ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate;
- 6-Chloro-N-[(3S)-1-[(1S)-2-(2-{[(2-hydroxypropyl)amino]methyl}morpholin-4-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate;
- 35 6-Chloro-N-[(3S)-1-[(1S)-2-{2-[(dimethylamino)methyl]morpholin-4-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate ;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(piperidin-1-ylmethyl)morpholin-4-yl]ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide ;
- 40

- 6-Chloro-N-((3S)-1-[(1S)-2-(3,3-difluoropiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-(4,4-difluoropiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5 N-((3S)-1-[(1S)-2-Azetidin-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-(3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 10 N-((3S)-1-[(1S)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- 15 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- N-1-[(1S)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- N-((3S)-1-[(1S)-2-(2-Azabicyclo[2.2.2]oct-2-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 20 6-Chloro-N-((3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3R)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 25 6-Chloro-N-((3R)-1-[(1S)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3R)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3R)-1-[(1S)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 30 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)ethenesulfonamide formate;
- 35 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
- 5-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
- N2-[(E)-2-(4-Chlorophenyl)ethenyl]sulfonyl)-N2-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinamide;
- 40

- N2-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 N-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycine;
- 5 (E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethenesulfonamide;
 (E)-2-(4-Chlorophenyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)ethenesulfonamide;
 Methyl N-[(E)-2-(4-chlorophenyl)ethenyl]sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinate;
- 10 N-[(E)-2-(4-Chlorophenyl)ethenyl]sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycine;
 N-[(E)-2-(4-Chlorophenyl)ethenyl]sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycine;
- 15 N-[(3S)-1-[(1S)-2-(3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-2-[2-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(3-phenylpiperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 20 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 1-[(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoyl]-N,N-dimethylprolinamide;
- 25 Methyl 1-[(2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoyl]-L-prolinate;
 6-Chloro-N-[(3S)-1-[(1S)-2-[4-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- Methyl 1-[(2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoyl]piperidine-3-carboxylate;
- 30 N-[(3S)-1-[(1S)-2-(4-Acetylpiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-2-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 35 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-(2-methylpyrrolidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 1-[(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoyl]prolinamide;
- 6-Chloro-N-[(3S)-1-[(1S)-2-(3-isopropyltetrahydropyrimidin-1(2H)-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
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- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-[(2S)-2-(morpholin-4-ylmethyl)pyrrolidin-1-yl]-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(4,6,7,8-tetrahydro-5H-thieno[3,2-c]azepin-5-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(3,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-(3,4-dihydroquinolin-1(2H)-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-(3,4-dihydroisoquinolin-2(1H)-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 10 6-Chloro-N-((3S)-1-((1S)-2-(1,3-dihydro-2H-isoindol-2-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide
- 15 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(5-oxo-1,4-diazepan-1-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-thiomorpholin-4-ylethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 20 6-Chloro-N-((3S)-1-((1S)-2-(2,5-dihydro-1H-pyrrol-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-(2-methylmorpholin-4-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 25 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-(3,6-dihydropyridin-1(2H)-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-(3-hydroxyquinoxalin-1(2H)-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 30 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}prop-2-ynamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}-1H-pyrrole-2-carboxamide;
- 35 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}-1-methyl-1H-1,2,3-triazole-4-carboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}-1,3-thiazole-2-carboxamide;
- N1-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}-N2,N2-dimethylglycinamide;
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- Methyl 3-({1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-3-oxopropanoate;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide;
- 5 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pyridine-2-carboxamide ;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-4H-1,2,4-triazole-3-carboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-2-ethylbutanamide ;
- 10 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}prop-2-ynamide;
- 6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide compound with 4-chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulphonamide;
- 15 5'-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]ethenesulfonamide;
- 20 5-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide;
- N-[(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-3-(1H-tetraazol-5-yl)benzenesulfonamide;
- 4-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide;
- 25 (E)-2-(4-Chlorophenyl)-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]ethenesulfonamide;
- 5'-Chloro-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide;
- 30 5-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide;
- 5-Chloro-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide;
- 6-Fluoro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 35 5-Chloro-3-methyl-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide;
- 6-Chloro-N-ethyl-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;

- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(5-oxo-1,4-diazepan-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 5 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpiperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 10 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-2-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide hydrobromide;
- 15 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-2-(1,4-diazepan-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 20 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-[(2-methyl-1,3-thiazol-4-yl)methyl]naphthalene-2-sulfonamide;
- 25 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(pyridin-2-ylmethyl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(pyridin-4-ylmethyl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]-N-[(2-methyl-1,3-thiazol-4-yl)methyl]naphthalene-2-sulfonamide formate;
- 30 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]-N-(pyridin-4-ylmethyl)naphthalene-2-sulfonamide formate;
- N-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycine;
- 35 6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-[(2S)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;

- 6-Chloro-N-[(3S)-1-((1R)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 5 6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1R)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 10 N-[1-((2R)-2-{(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl}propanoyl)piperidin-3-yl]benzamide;
- 6-Chloro-N-[(3S)-1-((1R)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide;
- 15 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-[(2S)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- N-[(3S)-1-[(1R)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloro-N-
- 20 methylnaphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-(4-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 25 N-[1-((2R)-2-{(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl}propanoyl)piperidin-2-yl]methylbenzamide;
- 6-Chloro-N-[(3S)-1-[(1R)-2-(3-methoxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 30 6-Chloro-N-methyl-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-[(3R)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 35 6-Chloro-N-[(3R)-1-((1S)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide;
- 6-Chloro-N-(3,3-dimethyl-2-oxobutyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- Ethyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-
- 40 oxoethyl]-2-oxopyrrolidin-3-yl]glycinate;

- tert*-Butyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinate;
- N-[1-((2R)-2-[(3R)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl]benzamide;
- 5 N-[(3R)-1-[(1R)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloro-N-methylnaphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- N-Allyl-6-chloro-N-[1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide ;
- 10 Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]glycinate formate;
- N-[(6-Chloro-2-naphthyl)sulfonyl]-N-(1-{1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine formate ;
- 15 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]glycine;
- 6-Chloro-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- N-[1-[(2R)-2-[(3R)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]benzamide ;
- 20 N-[(3R)-1-[(1R)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide;
- 6-Chloro-N-[(3R)-1-[(1R)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 25 6-Chloro-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3R)-1-[(1R)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3R)-1-[(1R)-2-[2-[(diethylamino)methyl]piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 30 N-[(3R)-1-[(1R)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide;
- 6-Bromo-N-[1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 35 6-Chloro-N-methyl-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3R)-1-[(1R)-2-[2-[(diethylamino)methyl]piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide;
- N-[(3R)-1-[(1R)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloro-N-methylnaphthalene-2-sulfonamide;
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- 6-Chloro-N-methyl-N-((3R)-1-((1R)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-ethoxy-2-oxopropyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 5 6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-methoxypropyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 4-[(1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl)amino)methyl]-1-methylpyridinium iodide;
- 5-(6-Amino-5-methylpyridin-3-yl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide;
- 10 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-(1-{1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine formate ;
- (E)-2-(5-Chlorothiophen-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide;
- 15 5-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide;
- 5-Chloro-3-methyl-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide;
- 20 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
- N2-[(6-Chloro-1-benzothiophen-2-yl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 25 5-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
- N2-[(5-Chloro-1-benzothiophen-2-yl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-phenylnaphthalene-2-sulfonamide;
- 30 6-Chloro-N-(4-fluorophenyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-pyridin-4-yl)naphthalene-2-sulfonamide;
- 35 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-pyridin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-thien-3-yl)naphthalene-2-sulfonamide;
- N-[(3S)-1-[(1S)-2-[(3S)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate;
- 40

[illegible]

- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-N-(2-morpholin-4-ylethyl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-N-(2-pyrrolidin-1-ylethyl)naphthalene-2-sulfonamide formate;
- 5 6-Chloro-N-[2-(dimethylamino)ethyl]-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- N-[2-(((6-Chloro-2-naphthyl)sulfonyl)((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)amino)ethyl]acetamide;
- 6-Chloro-N-{2-oxo-1-[1-(pyrrolidin-1-ylcarbonyl)propyl]pyrrolidin-3-yl)naphthalene-2-
- 10 sulfonamide;
- 6-Chloro-N-((3R)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- 5-Chloro-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-1H-indole-2-sulfonamide;
- 15 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-
- 20 yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 25 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- 1-[(2S)-2-((3S)-3-(((6-Chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-3-carboxamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(3-(((trifluoromethyl)sulfonyl)amino)piperidin-1-
- 30 yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 1-[(2S)-2-((3S)-3-(((6-Chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-2-carboxamide;
- 1-[(2S)-2-((3S)-3-(((6-Chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-4-carboxamide;
- 35 5'-Chloro-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- 5'-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-
- 40 oxopyrrolidin-3-yl)ethenesulfonamide;

- (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 5'-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- 5 Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinate;
- 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide;
- N-((3S)-1-[(1S)-2-(3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-
- 10 chloronaphthalene-2-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- Methyl N-[(E)-2-(4-chlorophenyl)ethenyl]sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycinate;
- 15 (E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-
- 20 oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- N-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}acetamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[3-(1H-pyrrol-1-ylmethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 25 6-Chloro-N-((3S)-1-[(1S)-2-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(2-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[3-(trifluoromethyl)piperidin-1-yl]ethyl]-2-
- 30 oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-((3S)-1-[(1S)-2-(3-methoxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 35 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(4-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-(3-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-octahydroquinolin-1(2H)-yl-2-oxoethyl]-2-oxopyrrolidin-
- 40 3-yl)naphthalene-2-sulfonamide;

- 6-Chloro-N-((3S)-1-((1S)-2-(4-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5'-Chloro-N-((3R)-1-((1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl)-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- 5 (E)-2-(4-Chlorophenyl)-N-((3R)-1-((1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl)-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}prop-2-ynamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1-methyl-1H-pyrrole-3-carboxamide;
- 10 Methyl 4-({1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}amino)-4-oxobutanoate;
- 4-({1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}amino)-4-oxobutanoic acid;
- 15 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1H-1,2,4-triazole-3-carboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1-methyl-1H-pyrrole-2-carboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}propanamide;
- 20 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1H-pyrazole-3-carboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-2-ethylbutanamide;
- 25 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}cyclopentanecarboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}pentanediamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}pyrazine-2-carboxamide;
- 30 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1H-pyrazole-4-carboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}malonamide;
- 35 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-2-methylpropanamide;
- N-1-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-N-3,N-3-dimethyl-beta-alaninamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}succinamide;
- 40

- N-{(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide;
- N-{(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pyridine-2-carboxamide;
- 5 N-{(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}isonicotinamide;
- Methyl 3-{(3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-3-oxopropanoate;
- N-1-{(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-N-2-,N-2-dimethylglycinamide;
- 10 Benzyl (3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate;
- N-{(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide;
- 15 N-{(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pyridine-2-carboxamide;
- N-{(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}isonicotinamide;
- Methyl 3-{(3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-3-oxopropanoate;
- 20 N-1-{(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-N-2-N-2-dimethylglycinamide;
- 5'-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-2,2'-bithiophene-5-sulfonamide;
- 25 6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide;
- 6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide compound with 4-chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide (1:1);
- 30 6-Fluoro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide;
- 6-Chloro-N-(3-furylmethyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide;
- 35 6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-N-(pyridin-3-ylmethyl)naphthalene-2-sulfonamide formate;
- N-1-[(2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}benzamide;

- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide;
- N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinamide;
- 5 6-Chloro-N-(2-furylmethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(1,3-thiazol-2-ylmethyl)naphthalene-2-sulfonamide;
- Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-yl-2-oxopyrrolidin-3-yl]glycinate);
- 10 5'-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 15 N-{1-[(2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl]acetamide;
- 6-Chloro-N-methyl-N-((3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-((3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 20 N-[1-((2R)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino)-2-oxopyrrolidin-1-yl]propanoyl)piperidin-3-yl]acetamide;
- 6-Chloro-N-methyl-N-((3S)-1-[(1R)-1-methyl-2-oxo-2-(3-[(phenylsulfonyl)amino]methyl)piperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 25 6-Chloro-N-((3S)-1-[(1R)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-methylnaphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1R)-2-[2-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-methylnaphthalene-2-sulfonamide;
- 30 6-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- N-Allyl-6-chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 35 Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinate;
- N-[(6-Chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycine;

- 6-Chloro-*N*-{(3*S*)-1-[(1*R*)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide;
- 6-Chloro-*N*-methyl-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide;
- 5 6-Chloro-*N*-methyl-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-[(2*R*)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide;
- 6-Chloro-*N*-[(3*S*)-1-[(1*S*)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]-*N*-methylnaphthalene-2-sulfonamide;
- Methyl *N*-[(6-chloro-2-naphthyl)sulfonyl]-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}glycinate;
- 10 *N*-[(6-Chloro-2-naphthyl)sulfonyl]-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}glycine;
- N*-2-[(6-Chloro-2-naphthyl)sulfonyl]-*N*-2-[(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}glycinamide;
- 15 6-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-*N*-(2-oxobutyl)naphthalene-2-sulfonamide;
- N*-2-[(6-Chloro-2-naphthyl)sulfonyl]-*N*-2-[(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-[(2*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl}glycinamide;
- Methyl *N*-[(6-chloro-2-naphthyl)sulfonyl]-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-[(2*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl}glycinate formate;
- 20 6-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-[(2*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl}-*N*-(2-oxobutyl)naphthalene-2-sulfonamide;
- N*-[1-[(2*R*)-2-[(3*S*)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}benzamide;
- 25 6-Chloro-*N*-methyl-*N*-{(3*R*)-1-[(1*R*)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide;
- 6-Chloro-*N*-methyl-*N*-{(3*S*)-1-[(1*R*)-1-methyl-2-[(2*R*)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide;
- N*-{(3*S*)-1-[(1*R*)-2-[(1*R*,4*S*)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-6-chloro-*N*-methylnaphthalene-2-sulfonamide;
- 30 6-Chloro-*N*-{(3*S*)-1-[(1*S*)-2-[3-(ethylamino)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide;
- 6-Chloro-*N*-[(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-{3-[(1*H*-pyrrol-2-ylmethyl)amino]piperidin-1-yl}ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 35 6-Chloro-*N*-[(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-{3-[(pyridin-3-ylmethyl)amino]piperidin-1-yl}ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-*N*-[(3*S*)-1-[(1*S*)-2-{3-[(3-hydroxybutyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-*N*-[(3*S*)-1-[(1*S*)-1-methyl-2-oxo-2-{3-[(pyridin-4-ylmethyl)amino]piperidin-1-yl}ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 40 2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;

- N-((3S)-1-((1S)-2-(3-((2-Aminopyrimidin-5-yl)methyl)amino)piperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(3-((pyridin-2-ylmethyl)amino)piperidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(3-((1H-pyrazol-3-ylmethyl)amino)piperidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(3-((pyridin-4-ylmethyl)amino)piperidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-(3-((5-(hydroxymethyl)-2-furyl)methyl)amino)piperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 10 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(3-((1,3-thiazol-2-ylmethyl)amino)piperidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-(3-((1-methyl-1H-imidazol-2-yl)methyl)amino)piperidin-1-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 15 6-Chloro-N-((3S)-1-((1S)-2-(3-((3-hydroxy-2,2-dimethylpropyl)amino)piperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-(3-((1H-imidazol-4-ylmethyl)amino)piperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- Benzyl (3S)-1-((2S)-2-((3S)-3-((6-chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-ylcarbamate;
- 20 N-((3S)-1-((1S)-2-((3S)-3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- N-((3S)-1-((1S)-2-((3R)-3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 25 (E)-2-(5-Chlorothien-2-yl)-N-methyl-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 5-Chloro-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)thieno[3,2-b]pyridine-2-sulfonamide;
- 30 More preferred compounds of the invention include:
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide ;
- 35 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide ;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-(3,3-difluoropiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 40

- 6-Chloro-N-((3S)-1-[(1S)-2-(4,4-difluoropiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-(3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5 N-((3S)-1-[(1S)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- N-{1-[(1S)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-6-chloronaphthalene-2-sulfonamide;
- 10 N-((3S)-1-[(1S)-2-(2-Azabicyclo[2.2.2]oct-2-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide;
- 15 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)ethenesulfonamide formate;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
- 5-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
- 20 N2-[[E)-2-(4-Chlorophenyl)ethenyl]sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinamide;
- N2-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinamide ;
- 25 N-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycine;
- (E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)ethenesulfonamide;
- 30 Methyl N-[[E)-2-(4-chlorophenyl)ethenyl]sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinate;
- N-[[E)-2-(4-Chlorophenyl)ethenyl]sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycine;
- 35 N-((3S)-1-[(1S)-2-(3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-thiomorpholin-4-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}prop-2-ynamide;
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- N1-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-N2,N2-dimethylglycinamide;
Methyl 3-({1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}amino)-3-oxopropanoate;
- 5 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}nicotinamide;
N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}pyridine-2-carboxamide;
6-Chloro-N-ethyl-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 10 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-oxo-2-(5-oxo-1,4-diazepan-1-yl)ethyl]-2-oxopyrrolidin-3-yl}glycinamide;
N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide;
- 15 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl}glycinamide;
N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl}glycinamide;
N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide;
- 20 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-[(2-methyl-1,3-thiazol-4-yl)methyl]naphthalene-2-sulfonamide;
6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(pyridin-2-ylmethyl)naphthalene-2-sulfonamide formate;
- 25 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(pyridin-4-ylmethyl)naphthalene-2-sulfonamide formate;
6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-[(2-methyl-1,3-thiazol-4-yl)methyl]naphthalene-2-sulfonamide formate;
- 30 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(pyridin-4-ylmethyl)naphthalene-2-sulfonamide formate;
N-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}glycine;
N-[1-((2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl]benzamide;
- 35 6-Chloro-N-(3,3-dimethyl-2-oxobutyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
tert-Butyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinate;

- N-Allyl-6-chloro-N-{1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide ;
- N-[(6-Chloro-2-naphthyl)sulfonyl]-N-(1-{1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine formate;
- 5 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-((3S)-1-{(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine;
- 6-Chloro-N-methyl-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide;
- N-[(6-Chloro-2-naphthyl)sulfonyl]-N-(1-{1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine formate ;
- 10 (E)-2-(5-Chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
- 15 N2-[(6-Chloro-1-benzothien-2-yl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 6-Chloro-N-[(3S)-1-[(1S)-2-[(1R,5S)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-[(1R,5S)-7-[2-(methylamino)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 20 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-[(1R,5S)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide trifluoroacetate;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide formate;
- 25 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 30 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 35 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-morpholin-4-ylethyl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-pyrrolidin-1-ylethyl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-[2-(dimethylamino)ethyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate;
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- N-[2-([(6-Chloro-2-naphthyl)sulfonyl]((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)amino)ethyl]acetamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 5 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 10 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
 15 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
 5'-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
 Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinate;
 20 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide;
 N-((3S)-1-[(1S)-2-(3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
 25 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
 Methyl N-([(E)-2-(4-chlorophenyl)ethenyl]sulfonyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycinate;
 (E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
 30 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 6-Chloro-N-((3S)-1-[(1S)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 35 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}acetamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[3-(1H-pyrrol-1-ylmethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 6-Chloro-N-((3S)-1-[(1S)-2-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
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- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}prop-2-ynamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-1-methyl-1H-pyrrole-3-carboxamide;
- 5 Methyl 4-({1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-4-oxobutanoate;
- 4-({1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-4-oxobutanoic acid;
- N-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide;
- 10 N-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pyridine-2-carboxamide;
- N-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}isonicotinamide;
- 15 Methyl 3-((3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-3-oxopropanoate;
- N-1-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-N-2,N-2-dimethylglycinamide;
- Benzyl (3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate;
- 20 N-((3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide;
- N-((3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}isonicotinamide;
- 25 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide ;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1-benzothiophene-2-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide;
- 30 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1-benzothiophene-2-sulfonamide compound with 4-chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1-benzothiophene-2-sulfonamide (1:1);
- 6-Chloro-N-(3-furylmethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 35 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(pyridin-3-ylmethyl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide;

- N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 6-Chloro-N-(2-furylmethyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 5 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(1,3-thiazol-2-ylmethyl)naphthalene-2-sulfonamide;
 Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinate;
 5'-Chloro-N-(cyanomethyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide;
 10 6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-methyl-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 15 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 N-[1-((2R)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]acetamide;
 6-Chloro-N-(cyanomethyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 20 6-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 N-Allyl-6-chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 25 Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinate;
 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycine;
 6-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 30 6-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinate;
 35 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycine;
 N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)naphthalene-2-sulfonamide;
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- N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)glycinamide;
 Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)glycinate formate;
 5 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide;
 N-[1-((2R)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]benzamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-{3-[(1H-pyrrol-2-ylmethyl)amino]piperidin-1-yl}ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 10 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-{3-[(pyridin-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-{3-[(1H-pyrazol-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 15 Benzyl (3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate;
 N-((3S)-1-[(1S)-2-[(3S)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide; and
 N-((3S)-1-[(1S)-2-[(3R)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-
 20 chloronaphthalene-2-sulfonamide.

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Preferred compounds of the invention also include:

- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 30 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 35 6-Chloro-N-[(3S)-1-[(1S)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;

- 1-[(2S)-2-((3S)-3-[[6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidine-3-carboxamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-(3-[[trifluoromethyl)sulfonyl]amino]piperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5 1-[(2S)-2-((3S)-3-[[6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidine-2-carboxamide;
 1-[(2S)-2-((3S)-3-[[6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidine-4-carboxamide;
 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- 10 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 15 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
 5'-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
 Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinate;
- 20 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide;
 N-((3S)-1-[(1S)-2-(3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 25 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
 Methyl N-[(E)-2-(4-chlorophenyl)ethenyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycinate;
 (E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 30 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 6-Chloro-N-((3S)-1-[(1S)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 35 N-[(1-[(2S)-2-((3S)-3-[[6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl)acetamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[3-(1H-pyrrol-1-ylmethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 6-Chloro-N-((3S)-1-[(1S)-2-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
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- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(2-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[3-(trifluoromethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-((3S)-1-[(1S)-2-(3-methoxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(4-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 10 6-Chloro-N-((3S)-1-[(1S)-2-(3-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-octahydroquinolin-1(2H)-yl]-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 15 6-Chloro-N-((3S)-1-[(1S)-2-(4-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5'-Chloro-N-((3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-((3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide;
- 20 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}prop-2-ynamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1-methyl-1H-pyrrole-3-carboxamide;
- 25 *tert*-Butyl 1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-ylcarbamate;
- Methyl 4-({1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}amino)-4-oxobutanoate;
- 4-({1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}amino)-4-oxobutanoic acid;
- 30 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1H-1,2,4-triazole-3-carboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1-methyl-1H-pyrrole-2-carboxamide;
- 35 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}propanamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1H-pyrazole-3-carboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-2-ethylbutanamide;
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- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}cyclopentanecarboxamide;
 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pentanediamide;
 5 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pyrazine-2-carboxamide;
 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-1H-pyrazole-4-carboxamide;
 N-{1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}malonamide;
 10 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-2-methylpropanamide;
 N-1-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-N-3-,N-3-dimethyl-beta-alaninamide;
 15 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}succinamide;
 N-{(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide;
 N-{(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pyridine-2-carboxamide;
 20 N-{(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}isonicotinamide;
 Methyl 3-({(3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-3-oxopropanoate;
 25 N-1-({(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-N-2-,N-2-dimethylglycinamide;
 Benzyl (3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate;
 N-{(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide;
 30 N-{(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pyridine-2-carboxamide;
 N-{(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}isonicotinamide;
 35 Methyl 3-({(3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-3-oxopropanoate;
 N-1-({(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-N-2-N-2-dimethylglycinamide;
 5'-Chloro-N-({(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-2,2'-
 40 bithiophene-5-sulfonamide;

- 4'-Fluoro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1,1'-biphenyl-4-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1-benzothiophene-2-sulfonamide;
- 5 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1-benzothiophene-2-sulfonamide compound with 4-chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1-benzothiophene-2-sulfonamide (1:1);
- 10 6-Fluoro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-(3-furylmethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-
- 15 (pyridin-3-ylmethyl)naphthalene-2-sulfonamide formate;
- N-{1-[(2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}benzamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide;
- 20 N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinamide;
- 6-Chloro-N-(2-furylmethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(1,3-
- 25 thiazol-2-ylmethyl)naphthalene-2-sulfonamide;
- Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycinate;
- 5'-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- 30 6-Chloro-N-((3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- N-{1-[(2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}acetamide;
- 6-Chloro-N-methyl-N-((3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-
- 35 yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-((3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- N-[1-((2R)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}acetamide;

- 6-Chloro-N-methyl-N-((3S)-1-[(1R)-1-methyl-2-oxo-2-(3-
{[(phenylsulfonyl)amino]methyl}piperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-
sulfonamide;
- 6-Chloro-N-((3S)-1-[(1R)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-
5 oxopyrrolidin-3-yl)-N-methylnaphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1R)-2-[2-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-
oxopyrrolidin-3-yl)-N-methylnaphthalene-2-sulfonamide;
- 6-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-
oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 10 6-Chloro-N-methyl-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-
yl)naphthalene-2-sulfonamide;
- N-Allyl-6-chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-
yl)naphthalene-2-sulfonamide;
- Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-
15 oxoethyl]-2-oxopyrrolidin-3-yl)glycinate;
- N-[(6-Chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-
oxopyrrolidin-3-yl)glycine;
- 1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-
yl)propanoyl]piperidine-2-carboxylic acid;
- 20 6-Chloro-N-((3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-
yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-
yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-((3S)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-
25 oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-2-[2-[(diethylamino)methyl]piperidin-1-yl]-1-methyl-2-oxoethyl]-2-
oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide;
- Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-
ylethyl]-2-oxopyrrolidin-3-yl)glycinate;
- 30 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-
oxopyrrolidin-3-yl)glycine;
- 6-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-
oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-
35 oxopyrrolidin-3-yl)glycinamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-N-(2-
oxobutyl)naphthalene-2-sulfonamide;
- N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-
ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)glycinamide;

- Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)glycinate formate;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide;
- 5 N-[1-((2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl]benzamide;
- 6-Chloro-N-methyl-N-((3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-((3S)-1-((1R)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 10 N-((3S)-1-((1R)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-6-chloro-N-methylnaphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-[3-(ethylamino)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 15 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1H-pyrrol-2-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-hydroxybutyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 20 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-4-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- N-((3S)-1-[(1S)-2-(3-[(2-Aminopyrimidin-5-yl)methyl]amino)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide;
- 25 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-2-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1H-pyrazol-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-4-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 30 6-Chloro-N-((3S)-1-((1S)-2-[3-({[5-(hydroxymethyl)-2-furyl]methyl}amino)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1,3-thiazol-2-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 35 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(3-[(1-methyl-1H-imidazol-2-yl)methyl]amino)piperidin-1-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-hydroxy-2,2-dimethylpropyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-((1S)-2-{3-[(1H-imidazol-4-ylmethyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 40

Benzyl (3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate;

N-((3S)-1-[(1S)-2-[(3S)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;

- 5 N-((3S)-1-[(1S)-2-[(3R)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide.

More preferred compounds of the invention also include:

- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 10 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- 15 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-[(3S)-1-[(1S)-2-[2-[(diethylamino)methyl]piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- 20 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 25 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 5'-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinate;
- 30 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide;
- N-((3S)-1-[(1S)-2-(3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- 35 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- Methyl N-[(E)-2-(4-chlorophenyl)ethenylsulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycinate;
- (E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 40

- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}acetamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[3-(1H-pyrrol-1-ylmethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-
- 10 3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- (E)-2-(4-Chlorophenyl)-N-((3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 15 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}prop-2-ynamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}-1-methyl-1H-pyrrole-3-carboxamide;
- Methyl 4-({1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-
- 20 yl]propanoyl}piperidin-3-yl}amino)-4-oxobutanoate;
- 4-({1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}amino)-4-oxobutanoic acid;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}-1H-1,2,4-triazole-3-carboxamide;
- 25 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}-1-methyl-1H-pyrrole-2-carboxamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}-2-ethylbutanamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-
- 30 yl]propanoyl}piperidin-3-yl}pyrazine-2-carboxamide;
- N-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}nicotinamide;
- N-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}pyridine-2-carboxamide;
- 35 N-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}isonicotinamide;
- Methyl 3-((3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}amino)-3-oxopropanoate;
- N-1-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-
- 40 yl]propanoyl}piperidin-3-yl)-N-2-,N-2-dimethylglycinamide;

- Benzyl (3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate;
 N-[(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]nicotinamide;
 5 N-[(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]pyridine-2-carboxamide;
 N-[(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]isonicotinamide;
 5'-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-
 10 bithiophene-5-sulfonamide ;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide;
 (E)-2-(4-Chlorophenyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide;
 15 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide compound with 4-chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide (1:1);
 6-Chloro-N-(3-furylmethyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 20 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(pyridin-3-ylmethyl)naphthalene-2-sulfonamide formate;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)naphthalene-2-sulfonamide;
 N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 25 2-oxopyrrolidin-3-yl]glycinamide;
 6-Chloro-N-(2-furylmethyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(1,3-thiazol-2-ylmethyl)naphthalene-2-sulfonamide;
 30 Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinate;
 5'-Chloro-N-(cyanomethyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 35 6-Chloro-N-methyl-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;

- N-[1-((2R)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl]acetamide;
 6-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 5 6-Chloro-N-methyl-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 N-Allyl-6-chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinate;
 10 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycine;
 6-Chloro-N-methyl-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 15 6-Chloro-N-methyl-N-((3S)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-2-[(diethylamino)methyl]piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide;
 Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycinate;
 20 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycine;
 6-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 25 N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycinamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide;
 N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)glycinamide;
 30 Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)glycinate formate;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide;
 35 N-[1-((2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl]benzamide;
 6-Chloro-N-methyl-N-((3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 6-Chloro-N-methyl-N-((3S)-1-[(1R)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
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- 6-Chloro-N-((3S)-1-((1S)-2-[3-(ethylamino)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1H-pyrrol-2-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 5 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-hydroxybutyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 N-[(3S)-1-[(1S)-2-(3-[(2-Aminopyrimidin-5-yl)methyl]amino)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide;
 10 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1H-pyrazol-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-hydroxy-2,2-dimethylpropyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 15 N-((3S)-1-((1S)-2-[(3S)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
 N-((3S)-1-((1S)-2-[(3R)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide.
- 20 The compounds of formula (I), (Ia), (Ib), or (Ic), including pharmaceutically acceptable derivatives thereof, are Factor Xa inhibitors and as such are useful in the treatment of clinical conditions susceptible to amelioration by administration of a Factor Xa inhibitor. Such conditions include acute vascular diseases such as coronary thrombosis (for example myocardial infarction and unstable angina), thromboembolism, acute vessel closure
 25 associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke; in oedema and PAF mediated inflammatory diseases such as adult respiratory shock syndrome, septic shock
 30 and reperfusion damage; the treatment of pulmonary fibrosis; the treatment of tumour metastasis; neurodegenerative disease such as Parkinson's and Alzheimer's diseases; viral infection; Kasabach Merritt Syndrome; Haemolytic uremic syndrome; arthritis; osteoporosis; as anti-coagulants for extracorporeal blood in for example, dialysis, blood filtration, bypass, and blood product storage; and in the coating of invasive devices such as prostheses,
 35 artificial valves and catheters in reducing the risk of thrombus formation.

Preferably, the condition susceptible to amelioration by a Factor Xa inhibitor is selected from coronary thrombosis (for example myocardial infarction and unstable angina), pulmonary embolism, deep vein thrombosis and the prevention of thromboembolic events associated
 40 with atrial fibrillation, e.g. stroke.

Accordingly, one aspect of present invention provides a compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof for use in medical therapy, particularly for use in the amelioration of a clinical condition in a mammal, including a human, for which a Factor Xa inhibitor is indicated.

In another aspect, the invention provides a method for the treatment and/or prophylaxis of a mammal, including a human, suffering from a condition susceptible to amelioration by a Factor Xa inhibitor which method comprises administering to the subject an effective amount of a compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof.

In another aspect, the present invention provides the use of a compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of a condition susceptible to amelioration by a Factor Xa inhibitor.

It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

While it is possible that, for use in therapy, a compound of the present invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

In a further aspect, the invention provides a pharmaceutical composition comprising at least one compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Accordingly, the present invention further provides a pharmaceutical formulation comprising at least one compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof, thereof in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In another aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, at least one compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable carrier

and/or excipient for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier and/or excipient.

The compounds for use according to the present invention may be formulated for oral, buccal, parenteral, topical, rectal or transdermal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions or they may be presented as a dry product for constitution with water or other suitable vehicles before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in a conventional manner.

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The compounds according to the present invention may be formulated for parenteral administration by injection, e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such

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as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

- 5 The compounds according to the present invention may be formulated for topical administration by insufflation and inhalation. Examples of types of preparation for topical administration include sprays and aerosols for use in an inhaler or insufflator.

Powders for external application may be formed with the aid of any suitable powder base, for
10 example, lactose, talc or starch. Spray compositions may be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as metered dose inhalers, with the use of a suitable propellant.

The compounds according to the present invention may also be formulated in rectal
15 compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation
20 (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds according to the present invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

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A proposed dose of the compounds according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 1g, preferably to 1mg to 500mg of the active ingredient per unit dose, expressed as the weight of free base. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of
30 administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. The dosage will also depend on the route of administration. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

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The compounds of formula (I), (Ia), (Ib), or (Ic) may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

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When a compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. The compounds of the present invention may be used in combination with other
5 antithrombotic drugs such as thrombin inhibitors, thromboxane receptor antagonists, prostacyclin mimetics, phosphodiesterase inhibitors, fibrinogen antagonists, thrombolytic drugs such as tissue plasminogen activator and streptokinase, non-steroidal anti-inflammatory drugs such as aspirin, and the like.

- 10 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical
15 formulations by any convenient route.

When administration is sequential, either the Factor Xa inhibitor or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

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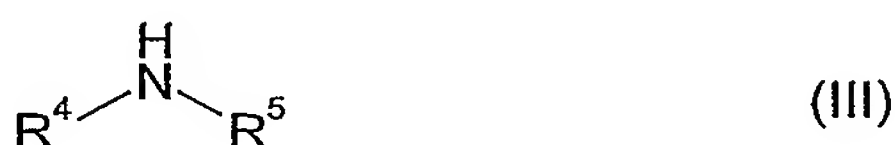
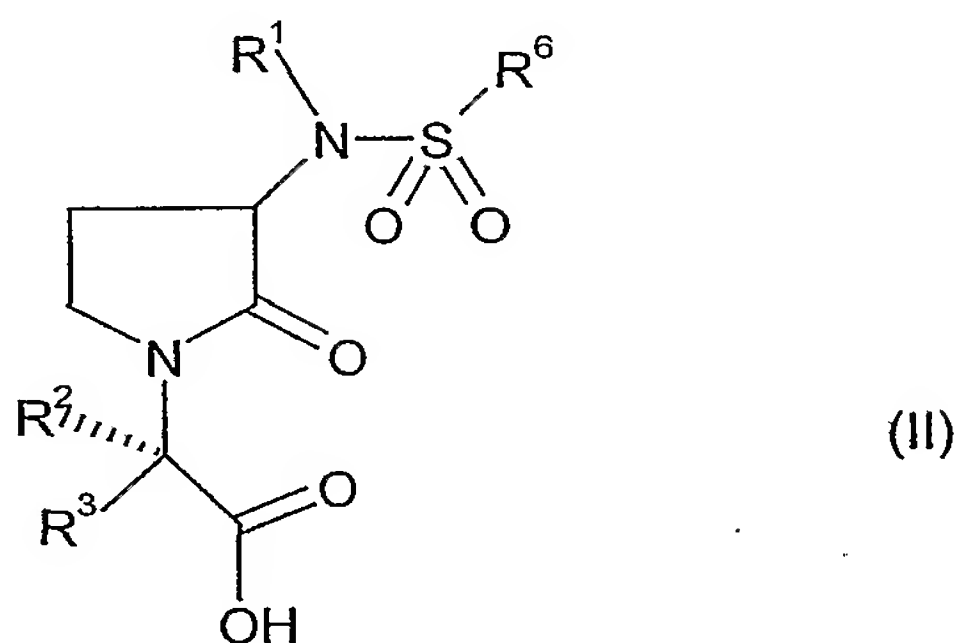
When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

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- When a compound of formula (I), (Ia), (Ib), or (Ic) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will
30 be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

- The compounds of formula (I), (Ia), (Ib), or (Ic) and physiologically acceptable salts or solvates thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups are as defined above for compounds of formula (I), (Ia), (Ib), or (Ic) unless otherwise stated.
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According to a further aspect of the present invention, there is provided a process (A) for preparing a compound of formula (I), (Ia), (Ib), or (Ic), which process comprises reacting a compound of formula (II) with a compound of formula (III).



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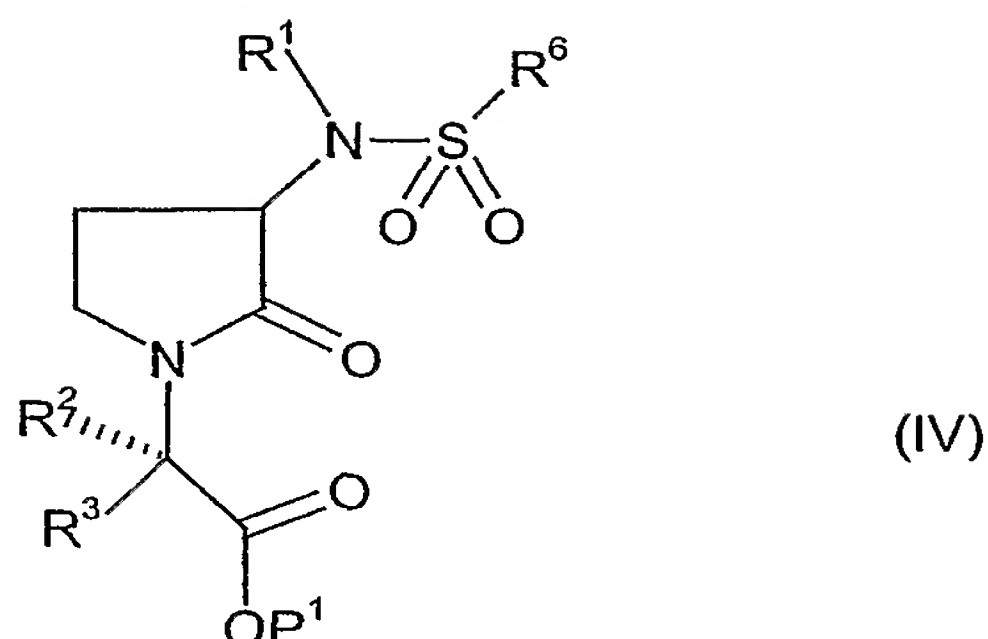
Suitably, the reaction may be carried out in the presence of a coupling agent, for example 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride, HOBt (1-hydroxybenzotriazole), a base, e.g. Et₃N (triethylamine), and an organic solvent, e.g. DCM (dichloromethane), suitably at room temperature.

It will be appreciated by persons skilled in the art that compounds of formula (I), (Ia), (Ib), or (Ic) may be prepared by interconversion, utilising other compounds of formula (I), (Ia), (Ib), or (Ic), which are optionally protected by standard protecting groups, as precursors. For instance, compounds of formula (I) or (Ib) where R⁴ and R⁵ together with the N atom to which they are bonded, form a 5-, 6- or 7- membered non-aromatic heterocyclic ring substituted by -NH₂, may be converted into compounds of formula (I) or (Ib) possessing alternative substituents on the heterocyclic ring, e.g. -NHCOR^d, -NR^bR^d, -NHCOR^e and/or -NHC₁₋₃alkylene-R^e, by methods well known in the art (see for example March, J., Advanced Organic Chemistry, John Wiley & Sons). Similarly, compounds of formula (Ia) where B represents -C₁₋₃alkylNH₂, may be converted into compounds of formula (Ia) possessing alternative substituents on the heterocyclic ring, e.g. -C₁₋₃alkylNR^bR^c, by methods well known in the art.

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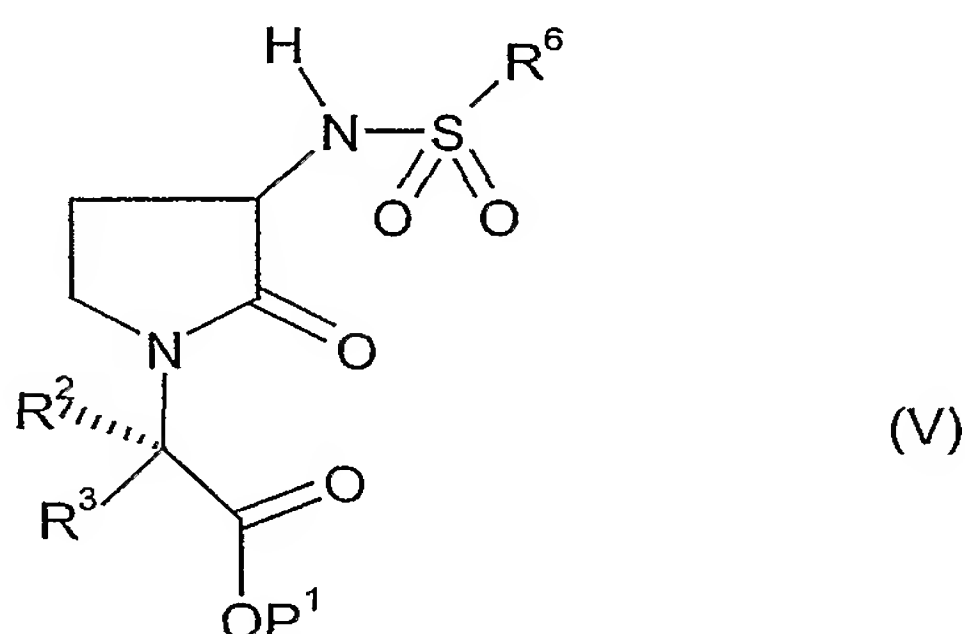
Compounds of formula (II) may be prepared from compounds of formula (IV):

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wherein P¹ is a suitable carboxylic acid protecting group, e.g. t-Butyl, by removal of the protecting group under standard conditions. For example, when P¹ represents t-Butyl, removal of the protecting group may be effected under acidic conditions, using for example TFA (trifluoroacetic acid) in a solvent such as DCM.

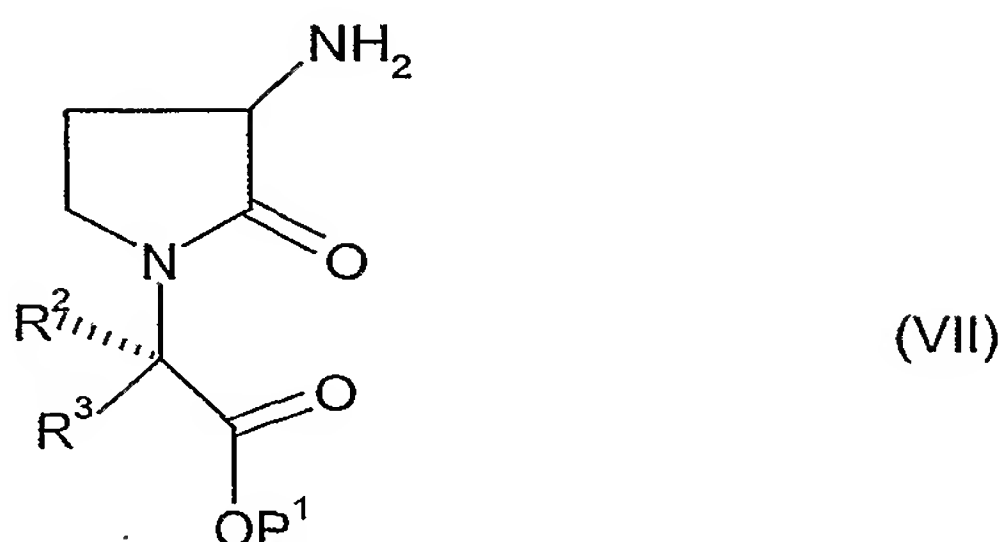
A compound of formula (IV) may be prepared by reacting a compound of formula (V) with a compound of formula (VI) where P¹ is as described above:



Suitably, where X is a leaving group such as a halogen atom, e.g. bromine, the reaction is carried out in the presence of a base, e.g. LiHMDS (lithium hexamethyldisilylamide), potassium carbonate or sodium carbonate. Preferably, the reaction is effected in a suitable organic solvent, e.g. THF, DMF, at a temperature from -78°C to +50°C, preferably -78°C to +20°C.

Alternatively, where X is hydroxy, the coupling reaction is carried out using standard reagents such as DIAD (diisopropyl azodicarboxylate) and n-Bu₃P (tri n-butyl phosphine) in a solvent such as tetrahydrofuran, suitably at room temperature:

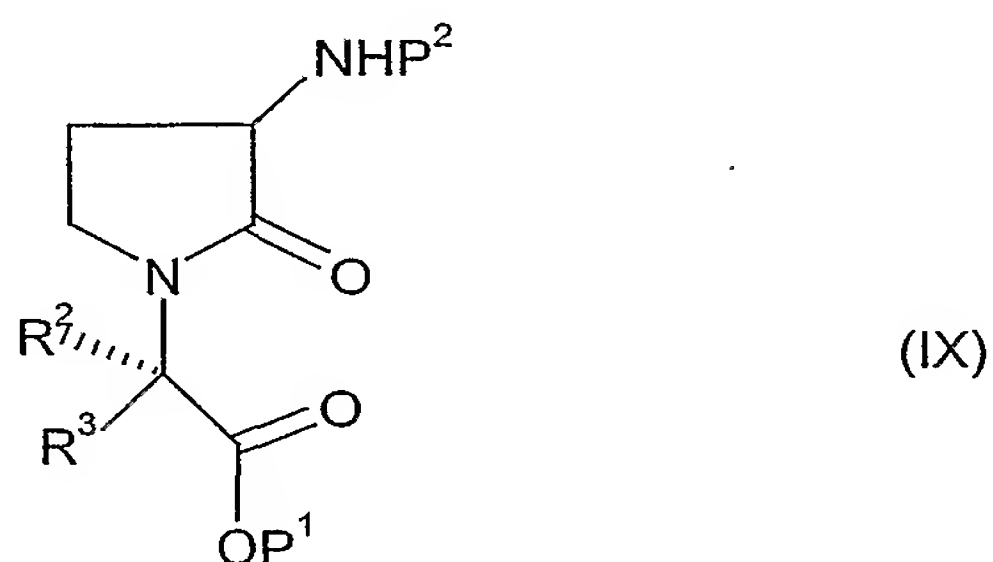
A compound of formula (V) may be prepared by reacting a compound of formula (VII) with a compound of formula (VIII):



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wherein T is a reactive group, such as a halide, preferably chloride, and P¹ is as described above. The reaction is conveniently carried out in the presence of a base, e.g. pyridine, and in a suitable solvent, e.g. DCM, suitably at room temperature.

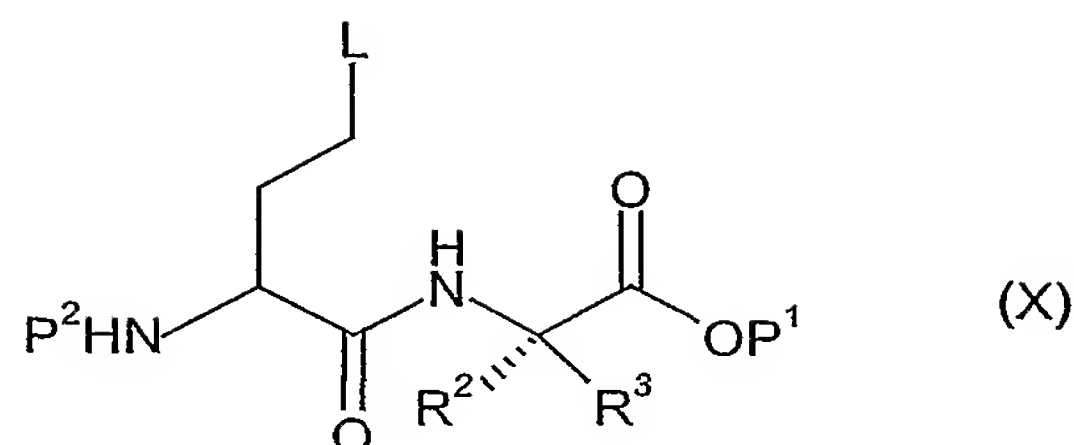
10 A compound of formula (VII) may be prepared from a compound of formula (IX)



where P¹ is as described above and P² represents a suitable amine protecting group, e.g. Cbz (benzyloxycarbonyl), by removal of the protecting group under standard conditions. For example, the protecting group may be removed by reaction with hydrogen in the presence of a metal catalyst, e.g. palladium/charcoal at atmospheric pressure. Suitably, the reaction is carried out in an alcoholic solvent, e.g. ethanol, suitably at room temperature.

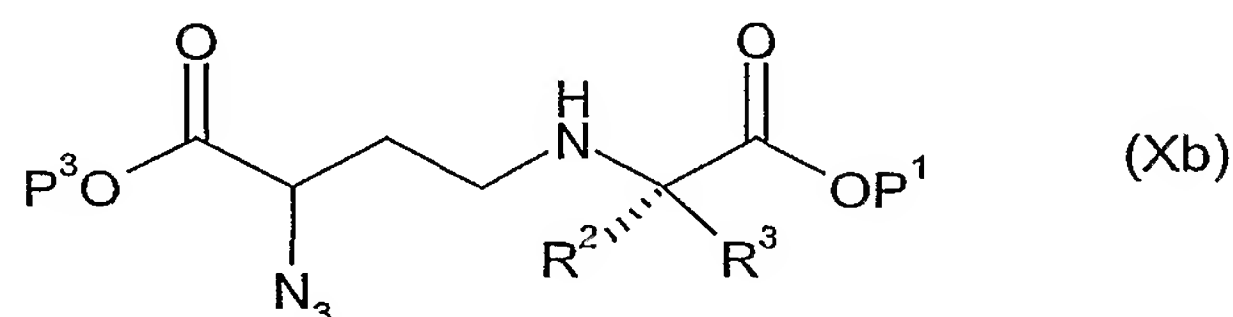
20 A compound of formula (IX) may be prepared from a compound of formula (X)

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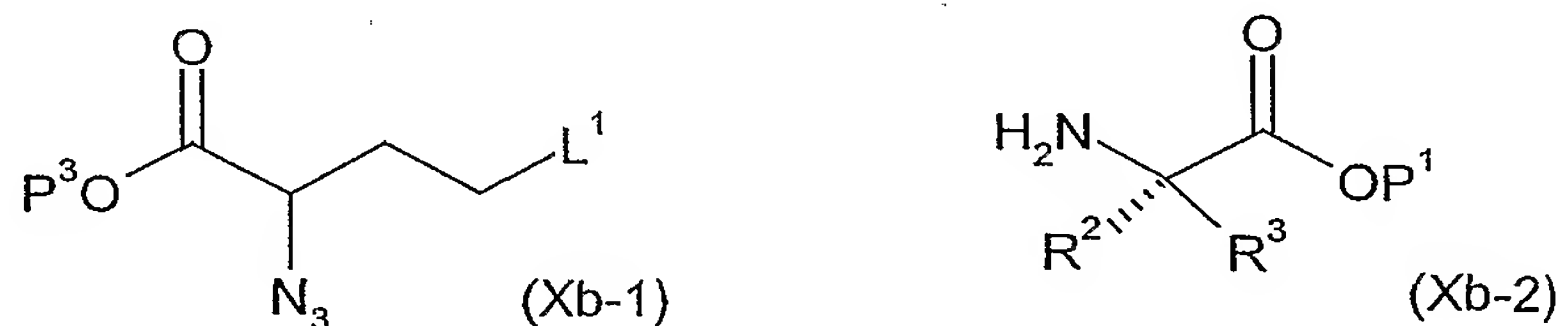
by cyclisation, wherein P^1 and P^2 are as described above and L represents a leaving group, e.g. $SMeRX$. The ring closure may be performed by treatment with Dowex 2 x 8 400 mesh OH^- resin in a suitable solvent, e.g. MeCN (acetonitrile). Alternatively, the ring closure may be performed by treatment with potassium carbonate in a suitable solvent, e.g. MeCN. Generally R will represent alkyl or aralkyl and X will represent halide, especially iodide or sulphate.

10 Alternatively, a compound of formula (IX) may be prepared from a compound of formula (Xb):



where P^1 and P^3 are protecting groups, by reaction with LiOH in a suitable solvent e.g. THF followed by reaction with DPPA (diphenylphosphoryl azide), a base e.g. Et_3N (triethylamine) in a suitable solvent e.g. DMF, suitably at room temperature to $70^\circ C$.

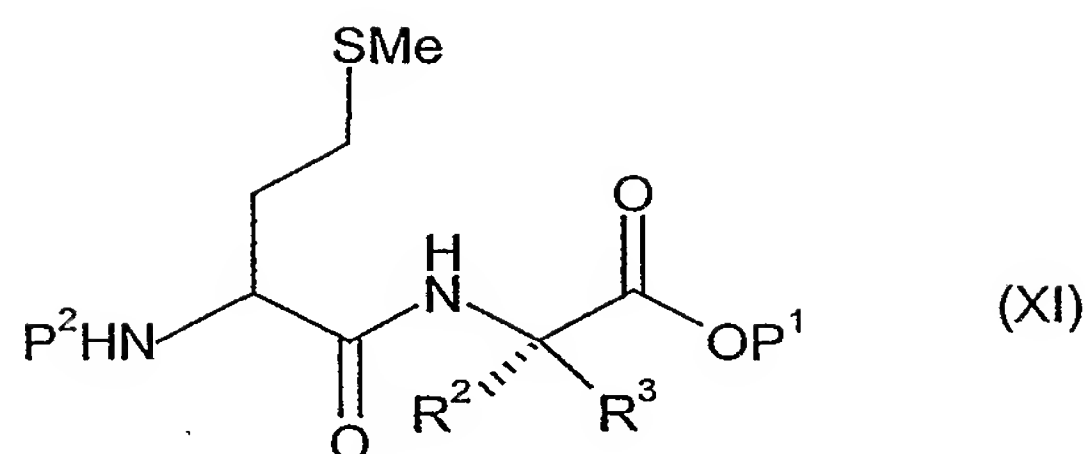
A compound of formula (Xb) may be prepared by reacting a compound of formula (Xb-1) with a compound of formula (Xb-2)



where L^1 is a leaving group e.g. bromine, in the presence of a base e.g. Et_3N in a suitable solvent e.g. MeCN.

A compound of formula (X) in which L represents $SMeRX$ may be formed from a compound of formula (XI)

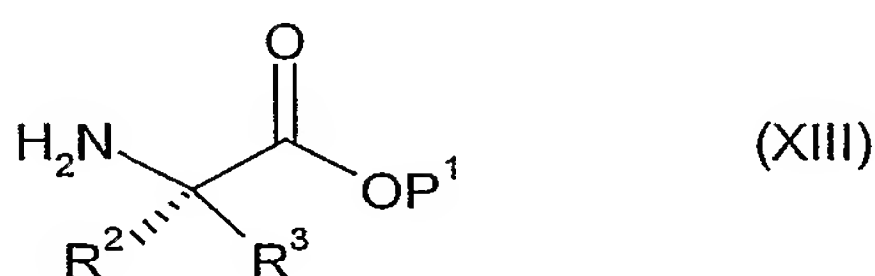
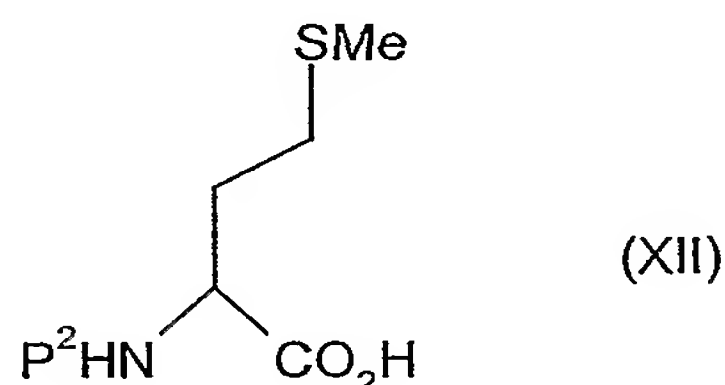
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by treatment with RX, where P^1 and P^2 are as described above and RX is a compound (e.g. MeI, benzyl iodide or Me_2SO_4) capable of converting sulphur in the SMe moiety to a sulphonium salt, in a suitable solvent, e.g. propanone or acetonitrile.

5

A compound of formula (XI) may be prepared by reacting a compound of formula (XII) with a compound of formula (XIII):



10

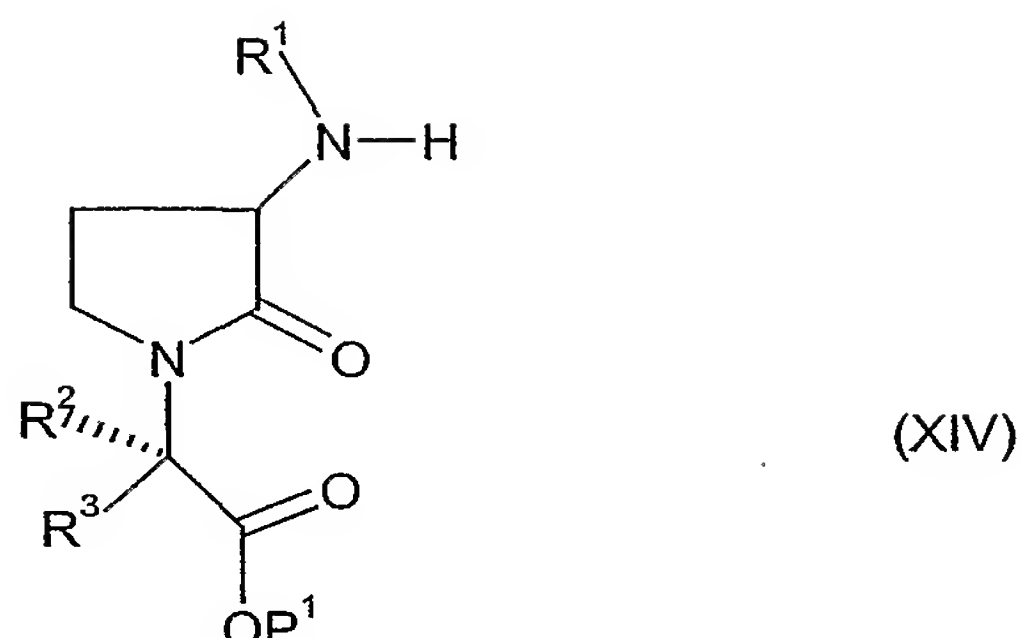
Suitably, the reaction may be carried out in the presence of a coupling agent, for example 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride, HOBt, a base, e.g. Et_3N , and an organic solvent, e.g. DCM, suitably at room temperature.

15

There is provided a further process (B) for preparing compounds of formula (IV) from compounds of formula (VII). According to process (B), a compound of formula (IV) may be prepared by reductive amination of a compound of formula (VII) with R^{1a}CHO (where R^{1a} is R^1 without a CH_2 linker directly attached to the N) using a suitable selective reducing agent to produce a compound of formula (XIV), followed by reaction with a compound of formula (VIII) in the presence of a base, e.g. pyridine, and in a solvent, e.g. DCM, suitably at room temperature.

20

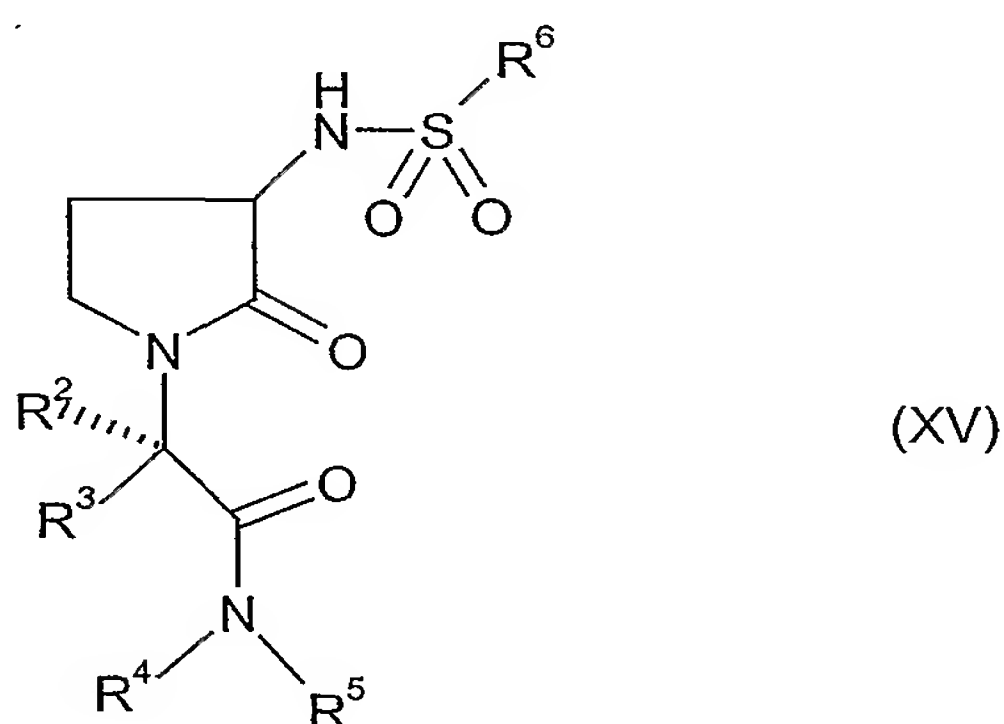
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The reductive amination is conveniently carried out by treatment with sodium triacetoxyborohydride in the presence of an acid such as acetic acid, in a solvent such as DCM, suitably at room temperature.

Compounds of formulae (III), (VI), (VIII), (Xb-1), (Xb-2), (X), (XI), (XII) and (XIII) are known compounds and/or can be prepared by processes well known in the art.

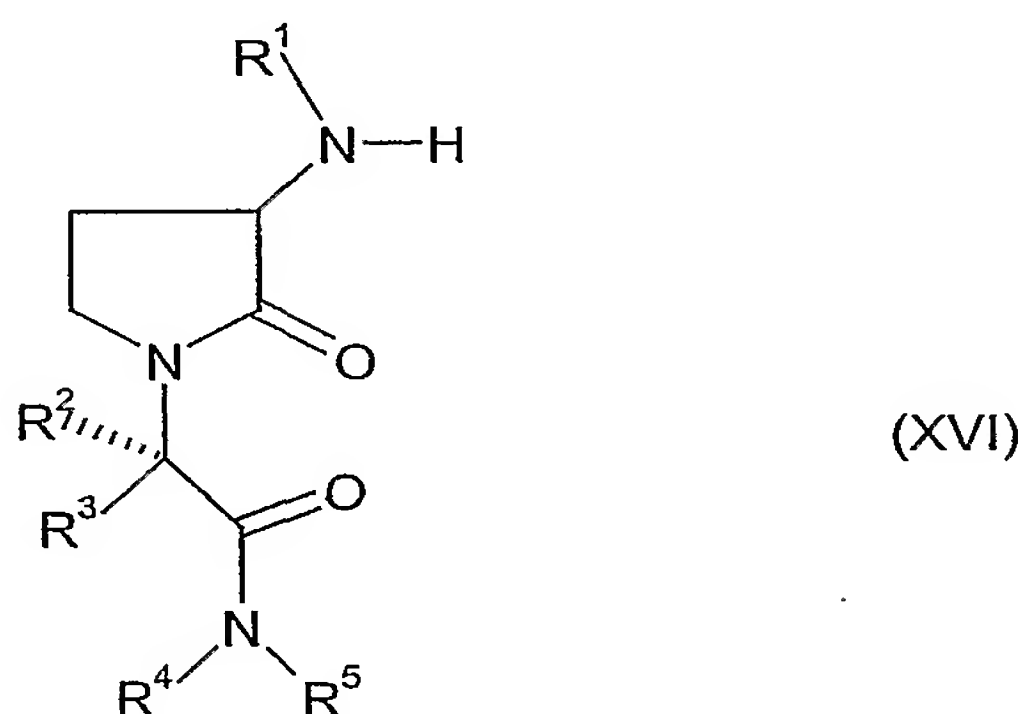
- 10 The various general methods described above may be useful for the introduction of the desired groups at any stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product. For example, those skilled in the art will appreciate that, with the use of appropriate protecting groups, the coupling to any of groups $-R^1$, $-SO_2R^6$ or $-NR^4R^5$ can be the final step in the preparation of a compound of formula (I), (Ia), (Ib), or (Ic). Hence, in another aspect of the invention, the final step in the preparation of a compound of formula (I), (Ia), (Ib), or (Ic) may comprise the coupling to group $-R^1$ by reacting a compound of formula (XV) with a compound of formula (VI):



76

Suitably, where X is a leaving group such as a halogen atom, e.g. bromine, the reaction is carried out in the presence of a base, e.g. LiHMDS (lithium hexamethyldisilylamide), potassium carbonate or sodium carbonate. Preferably, the reaction is effected in a suitable organic solvent, e.g. THF, DMF, at a temperature from -78°C to +50°C, preferably -78°C to +20°C.

In a further aspect of the present invention, the final step in the preparation of a compound of formula (I), (Ia), (Ib), or (Ic) may comprise the coupling to group -SO₂R⁶ by reacting a compound of formula (XVI) with a compound of formula (VIII):



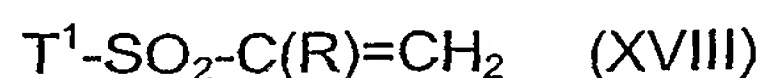
The reaction is conveniently carried out in the presence of a base, e.g. pyridine, and in a suitable solvent, e.g. DCM, suitably at room temperature.

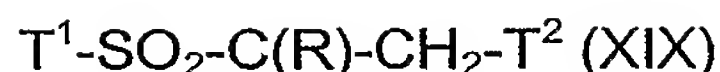
In a further aspect of the present invention, a compound of formula (I) where R¹ is an aryl or heteroaryl group may be prepared from a compound of formula (XV) by reaction with a compound of formula (XVII):



where C¹ is a suitable coupling group e.g. boronate [B(OH)₂] under metal catalysis, for example, with a copper salt such as copper(II) acetate, in the presence of an organic solvent e.g. DCM and a base, e.g. pyridine and optionally in the presence of molecular sieves.

In a further aspect of the present invention, a compound of formula (I) where R⁶ is -SO₂-CH=CH-aryl, SO₂-CH=CH-heteroaryl, SO₂-C(CH₃)=CH-aryl or SO₂-C(CH₃)=CH-heteroaryl may be prepared from a compound of formula (XVI) where R¹ is hydrogen, by reaction with a compound of formula (XVIII), or alternatively with a compound of formula (XIX):





where T^1 and T^2 are independently reactive groups, such as a halide, preferably chloride, in the presence of a base e.g. N,N-diisopropylethylamine and a suitable solvent e.g. MeCN, suitably at room temperature, to provide a compound of formula (XV) where R^6 is $C(R)=CH_2$, followed by reaction with a compound of formula (XX):



10

Where R^h is aryl or heteroaryl and L is a leaving group, e.g. bromine, in the presence of a base e.g. N,N-diisopropylethylamine, and a suitable solvent e.g. dioxane and a suitable transition metal catalyst e.g. di(palladium)tris(dibenzylideneacetone) and a suitable ligand e.g. 2-(di-t-butylphosphino)biphenyl under an inert atmosphere e.g. nitrogen, at a temperature 20-100°C preferably 40°C.

15

In a further aspect of the present invention, a compound of formula (I) where R^6 is a biaryl group may be prepared from a compound of formula (XVI) where R^1 is hydrogen and the amino group is optionally protected, for example, as a solid supported derivative derived from reductive amination under standard conditions, by reaction with a compound of formula of formula (XXI):

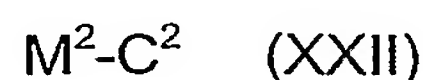
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25

wherein T is a reactive group, such as a halide, preferably chloride, and M^1 is an aryl or heteroaryl group with a suitable coupling group e.g. halogen, preferably bromide or iodide, in the presence of a suitable solvent e.g. DMF and a suitable base, e.g. N,N-diisopropylethylamine, followed by reaction with a compound of formula (XXII):

30



wherein M^2 is an aryl or heteroaryl group and C^2 is a suitable coupling group e.g. boronate $[B(OH)_2]$, in the presence of a metal catalyst e.g. tetrakis(triphenylphosphine)palladium(0), a base e.g. sodium carbonate, a suitable solvent e.g. THF and optionally in the presence of a cosolvent e.g. H_2O , followed by removal of any protecting groups under standard conditions, e.g. under standard conditions.

35

Those skilled in the art will appreciate that in the preparation of the compound of formula (I), (Ia), (Ib), or (Ic) or a solvate thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions. Suitable
5 protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl,
10 acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl type protecting groups (e.g. benzyl, trityl, chlorotriyl). Examples of suitable oxygen protecting groups may include for example alkyl silyl groups, such as trimethylsilyl or tert-
15 butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or tert-butyl; or esters such as acetate.

Various intermediate compounds used in the above-mentioned process, including but not limited to certain compounds of formulae (II), (IV), (V), (VII), (IX), (XIV), (XV) and
20 (XVI) are novel and accordingly constitute a further aspect of the present invention.

The present invention will now be further illustrated by the accompanying examples which should not be construed as limiting the scope of the invention in any way.

25

Examples

Abbreviations

	Boc	<i>t</i> -Butyloxycarbonyl
30	Cbz	Benzyloxycarbonyl
	THF	Tetrahydrofuran
	DCM	Dichloromethane
	DMF	N,N-Dimethylformamide
	HOBT	1-Hydroxybenzotriazole
35	br	broad
	m	multiplet
	q	quartet
	s	singlet
	t	triplet
40	d	doublet

Intermediate 1*tert*-Butyl N-[(benzyloxy)carbonyl]-L-methionyl-L-alaninate

Z-Protected L-methionine (10g) was dissolved in DMF (200ml) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (8.13g) was added followed by HOBT (5.72g) and triethylamine (19.7ml). The mixture was stirred for 1h then L-alanine *tert*-butyl ester (7.7g) was added and stirring continued for 18h. The mixture was concentrated under reduced pressure and partitioned between diethyl ether and water. The separated organic phase was washed with hydrochloric acid (1M), saturated sodium bicarbonate solution and brine, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (11.9g) as an orange oil which crystallised on standing.

Mass spectrum: Found: MH^+ 411

Intermediate 215 *tert*-Butyl N-[(benzyloxy)carbonyl]-D-methionyl-L-alaninate

Using Z-protected D-methionine, L-alanine *tert*-butyl ester, and the procedure described for Intermediate 1, the title compound was prepared.

Mass spectrum: Found: MH^+ 411

20 Intermediate 3 (RR)*tert*-Butyl N-[(benzyloxy)carbonyl]-D-methionyl-D-alaninate

Using Z-protected D-methionine, D-alanine *tert*-butyl ester and the procedure described for Intermediate 1, the title compound was prepared.

Mass spectrum: Found: MH^+ 411

25

Intermediate 4 (SR)*tert*-Butyl N-[(benzyloxy)carbonyl]-L-methionyl-D-alaninate

Using Z-protected L-methionine, D-alanine *tert*-butyl ester and the procedure described for Intermediate 1, the title compound was prepared.

30 Mass spectrum: Found: MH^+ 411Intermediate 5*tert*-Butyl (2S)-2-((3S)-3-[(benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

35 A solution of Intermediate 1 (11.9g) in acetone (75ml) was treated with methyl iodide (18ml) and stirred at room temperature for 72h. The reaction mixture was then concentrated under reduced pressure to give an orange solid which was dissolved in acetonitrile (200ml). Dowex (OH^- form) resin (19.42g) was added and the mixture stirred for 18h at room temperature. The mixture was filtered and the resin washed with ethyl acetate. The filtrate was concentrated under reduced pressure to afford a yellow oil which was purified by Biotage™

chromatography (eluting with cyclohexane:ethyl acetate 3:2) to give the title compound (2.92g) as a colourless oil.

Mass spectrum: Found: MH^+ 363

5 Intermediate 6

tert-Butyl (2S)-2-((3R)-3-[(benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

Using Intermediate 2 and the procedure described for Intermediate 5, the title compound was prepared.

Mass spectrum: Found: MH^+ 363

10

Intermediate 7

tert-Butyl (2R)-2-((3R)-3-[(benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

Using Intermediate 3 and the procedure described for Intermediate 5, the title compound was prepared.

15 Mass spectrum: Found: MH^+ 363

Intermediate 8

tert-Butyl (2R)-2-((3S)-3-[(benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

20 Using Intermediate 4 and the procedure described for Intermediate 5, the title compound was prepared.

Mass spectrum: Found: MH^+ 363

Intermediate 9

tert-Butyl (2S)-2-[(3S)-3-amino-2-oxopyrrolidin-1-yl]propanoate

25 A mixture of *tert*-butyl (2S)-2-((3S)-3-[(benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl)propanoate (2.82g), 10% palladium on carbon (0.3g) and ethanol (150ml) was stirred under an atmosphere of hydrogen for 18h. The reaction mixture was filtered through HarboliteTM and the filtrate was concentrated under reduced pressure to give the title compound (1.8g) as a pale yellow oil.

30 ¹H NMR (D₄MeOH): δ 4.56(1H, q), 3.57(1H, dd), 3.49-3.35(2H, 2 x m), 2.48-2.39(1H, m), 1.88-1.77(1H, m), 1.47(9H, s), 1.40 (3H, d) ppm.

Intermediate 10

tert-Butyl (2S)-2-[(3R)-3-amino-2-oxopyrrolidin-1-yl]propanoate

35 Using Intermediate 6 and the procedure described for Intermediate 9, the title compound was prepared.

¹H NMR (D₄MeOH): δ 4.60(1H, q), 3.58(1H, dd), 3.46(1H, dt), 3.41-3.33(1H, m), 2.48-2.40(1H, m), 1.82-1.70(1H, m), 1.45(9H, s), 1.40(3H, d) ppm.

40 Intermediate 11

tert-Butyl (2R)-2-[(3R)-3-amino-2-oxopyrrolidin-1-yl]propanoate

Using Intermediate 7 and the procedure described for Intermediate 9, the title compound was prepared.

¹H NMR (D₄MeOH): δ 4.58(1H, q), 3.75(1H, dd), 3.55-3.41(2H, 2 x m), 2.50(1H, m), 1.90(1H, m), 1.49(9H, s), 1.42(3H, d) ppm.

Intermediate 12tert-Butyl (2R)-2-[(3S)-3-amino-2-oxopyrrolidin-1-yl]propanoate

Using Intermediate 8 and the procedure described for Intermediate 9, the title compound was prepared.

¹H NMR (D₄MeOH): δ 4.68(1H, q), 3.78(1H, t), 3.56-3.40(2H, 2 x m), 2.52(1H, m), 1.89(1H, m), 1.48(9H, s), 1.42(3H, d) ppm.

Intermediate 13(2S)-2-((3S)-3-[(Benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl) propanoic acid

tert-Butyl (2S)-2-((3S)-3-[(benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl)propanoate (0.5g) was dissolved in DCM (7ml), and trifluoroacetic acid (4.7ml) was added. The mixture was stirred at room temperature for 1.5h and then concentrated under reduced pressure to give the title compound (0.423g) as a colourless oil which after azeotroping with toluene, crystallised.

Mass spectrum: Found: MH⁺ 307

Intermediate 14(2R)-2-((3R)-3-[(Benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl) propanoic acid

Using Intermediate 7 and the procedure described for Intermediate 13, the title compound was prepared.

Mass spectrum: Found: MH⁺ 307

Intermediate 15(2S)-2-((3R)-3-[(Benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl) propanoic acid

Using Intermediate 6 and the procedure described for Intermediate 13, the title compound was prepared.

Mass spectrum: Found: MH⁺ 307

Intermediate 16(2R)-2-((3S)-3-[(Benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl) propanoic acid

Using Intermediate 8 and the procedure described for Intermediate 13, the title compound was prepared.

Mass spectrum: Found: MH⁺ 307

Intermediate 17Benzyl (3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-ylcarbamate

To a solution of (2S)-2-((3S)-3-[[benzyloxy]carbonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid (3.1g) in DCM (30ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.6g), HOBt (3.2g) and triethylamine (2.5ml) and the mixture was stirred at room temperature for 5min. Piperidine (2.9ml) was added and the resultant mixture stirred at room temperature for 72h. The mixture was washed with potassium carbonate (2M), dried (over magnesium sulphate) and concentrated under reduced pressure. The residue was purified using BiotageTM chromatography (silica, eluting with cyclohexane:ethyl acetate 3:1 and then ethyl acetate) to give the title compound (2.6g) as a white solid.

Mass spectrum: Found: MH⁺ 374

Intermediate 18Benzyl (3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-ylcarbamate

Using Intermediate 14 and the procedure described for Intermediate 17, the title compound was prepared.

Mass spectrum: Found: MH⁺ 374

Intermediate 19Benzyl (3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-ylcarbamate

Using Intermediate 15 and the procedure described for Intermediate 17, the title compound was prepared.

Mass spectrum: Found: MH⁺ 374

Intermediate 20Benzyl (3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-ylcarbamate

Using Intermediate 16 and the procedure described for Intermediate 17, the title compound was prepared.

Mass spectrum: Found: MH⁺ 374

Intermediate 21(3R)-3-Amino-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]pyrrolidin-2-one

Using Intermediate 19 and the procedure described for Intermediate 9, the title compound was prepared.

Mass spectrum: Found: MH⁺ 240

Intermediate 22(3R)-3-Amino-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]pyrrolidin-2-one

Using Intermediate 18 and the procedure described for Intermediate 9, the title compound was prepared.

Mass spectrum: Found: MH^+ 240

Intermediate 23

(3S)-3-Amino-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]pyrrolidin-2-one

- 5 Using Intermediate 17 and the procedure described for Intermediate 9, the title compound was prepared.

Mass spectrum: Found: MH^+ 240

Intermediate 24

- 10 (3S)-3-Amino-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]pyrrolidin-2 one

Using Intermediate 20 and the procedure described for Intermediate 9, the title compound was prepared.

Mass spectrum: Found: MH^+ 240

- 15 Intermediate 25

tert-Butyl (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

- A solution of *tert*-butyl (2S)-2-[(3S)-3-amino-2-oxopyrrolidin-1-yl]propanoate (1.8g) in DCM (75ml) was treated with 6-chloronaphthylsulphonyl chloride¹ (2.28g) and pyridine (0.705ml) and stirred at room temperature for 72h. The mixture was washed with water and concentrated under reduced pressure to yield an oil which was purified by BiotageTM chromatography (eluting with cyclohexane:ethyl acetate 3:1) to give the title compound (2.31g), as a white solid.

Mass spectrum: Found: MH^+ 453

25

Intermediate 26

tert-Butyl (2S)-2-((3R)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

- Using Intermediate 10 and the procedure described for Intermediate 25, the title compound was prepared.

¹H NMR (CDCl₃): δ 8.45(1H, br.s), 7.96-7.83(4H, m), 7.56 (1H, dd), 5.41(1H, br.s), 4.66 (1H, q), 3.73(1H, dt), 3.42-3.34(2H, m), 2.62(1H, m), 2.01(1H, m), 1.38-1.32(12H, s+d) ppm.

Intermediate 27

- 35 tert-Butyl (2R)-2-((3R)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

Using Intermediate 11 and the procedure described for Intermediate 25, the title compound was prepared.

Mass spectrum: Found: MH^+ 453

40

Intermediate 28

tert-Butyl (2S)-2-[(3R)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl]propanoate

Using Intermediate 26 and methyl tosylate, and the procedure described for Intermediate 52,
5 the title compound was prepared.

Mass spectrum: Found: MH^+ 467

Intermediate 29

(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid

10 tert-Butyl (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoate (0.643g) was dissolved in DCM (19ml), and trifluoroacetic acid (19ml) was added. The mixture was stirred at room temperature for 2.5h and then concentrated under reduced pressure. Anhydrous DCM (4ml) was added and the solution concentrated under reduced pressure. Repetitive addition of DCM and concentration under reduced pressure
15 provided the title compound (0.56g) as a white foam.

Mass spectrum: Found: MH^+ 397

Intermediate 30

(2S)-2-[(3R)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl]propanoic acid
20 acid

Using Intermediate 28 and the procedure described for Intermediate 29, the title compound was prepared.

Mass spectrum: Found: MH^+ 411

25 Intermediate 31

(2S)-2-((3R)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid

Using Intermediate 26 and the procedure described for Intermediate 29, the title compound was prepared.

Mass spectrum: Found: MH^+ 397

30

Intermediate 32

(2R)-2-((3R)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid

Using Intermediate 27 and the procedure described for Intermediate 29, the title compound was prepared.

35 Mass spectrum: Found: MH^+ 397

Intermediate 33

tert-Butyl (2R)-2-(3-azido-2-oxopyrrolidin-1-yl)propanoate

To a solution of D-alanine *tert*-butylester (1.28g) and N, N-diisopropylethyamine (1.22ml) in
40 acetonitrile (15ml), was added a solution of ethyl 2-azido-4-bromobutanoate (1g) and sodium

iodide (0.02g) in acetonitrile (5ml). The mixture was heated at 60°C for 60h and then concentrated under pressure to give a brown oil. This oil was partitioned between DCM and water. The separated organic layer was washed further with water and dried (over magnesium sulphate), and concentrated under reduced pressure. The residual brown oil
5 was purified using BiotageTM chromatography (silica, eluting with cyclohexane;ethyl acetate 3:1) to give the title compound (0.204g) as a mixture of two diastereoisomers.
T.l.c. (cyclohexane:ethyl acetate, 2:1) R_f 0.20

Intermediate 34

10 tert-Butyl (2S)-2-(3-azido-2-oxopyrrolidin-1-yl)propanoate

Using ethyl 2-azido-4-iodobutanoate and L-alanine *tert*-butyl ester, and the procedure described for Intermediate 33, the title compound was prepared as a mixture of two diastereoisomers.

T.l.c. (cyclohexane:ethyl acetate, 3:1) R_f 0.15

15

Intermediate 35

tert-Butyl (2R)-2-(3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

A mixture of *tert*-butyl (2R)-2-(3-azido-2-oxopyrrolidin-1-yl)propanoate (0.035g), 10% palladium on carbon (0.003g) and ethanol (2ml) was stirred under an atmosphere of
20 hydrogen for 16h. The reaction mixture was filtered through HarboliteTM and the filtrate was concentrated under reduced pressure to give a yellow gum. The gum (0.026g) in DCM (2ml) was treated with 6-chloronaphthylsulphonyl chloride¹ (0.03g) and pyridine (0.02ml) and stirred at room temperature for 42h. The mixture was washed with water and concentrated under reduced pressure to yield an oil which was partially purified using SPE (aminopropyl,
25 eluting with methanol). The organic washings were concentrated under reduced pressure and the residue dissolved in DCM. The organic solution was purified by SPE (aminopropyl, eluting with methanol containing 10% v/v 2N HCl) to give the title compound (0.012g) as a white solid.

Mass spectrum: Found: MH⁺ 453

30

Intermediate 36

tert-Butyl (2S)-2-(3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

Using Intermediate 34 and the synthetic procedure described for Intermediate 35, the title compound was prepared.

35 Mass spectrum: Found: MH⁺ 453

Intermediate 37

(2R)-2-(3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid

Using Intermediate 35, and the synthetic procedure for Intermediate 13, the title compound
40 was prepared.

Mass spectrum: Found: MH^+ 411

Intermediate 38

(2S)-2-(3-((6-Chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoic acid

- 5 Using Intermediate 36, and the synthetic procedure for Intermediate 13, the title compound was prepared.

Mass spectrum: Found: MH^+ 411

Intermediate 39

- 10 (2R)-2-(3-((3'-Chloro-1,1'-biphenyl-4-yl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoic acid

Using Intermediate 33 and (3'-chloro-1,1'-biphenyl-4-yl)sulfonyl chloride and similar chemistry to that described for Intermediates 35 and 37, the title compound was prepared.

Mass spectrum: Found: MH^+ 424

- 15 Intermediate 40

(2R)-2-(3-((3-Chloroisoquinolin-7-yl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoic acid

Using Intermediate 33 and (3-chloroisoquinolin-7-yl)sulfonyl chloride and similar chemistry to that described for Intermediates 35 and 37, the title compound was prepared.

Mass spectrum: Found: MH^+ 398

20

Intermediates 41* and 42

tert-Butyl(2R)-2-((3R)-3-((6-chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoate (1)

tert-Butyl(2R)-2-((3S)-3-((6-chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-

- 25 yl)propanoate (2)

A mixture of *tert*-butyl (2R)-2-(3-azido-2-oxopyrrolidin-1-yl)propanoate (0.204g), 10% palladium on carbon (0.02g) and ethanol (10ml) was stirred under an atmosphere of hydrogen for 5h. The reaction mixture was filtered through HarboliteTM and the filtrate was concentrated under reduced pressure to give a yellow oil. The oil (0.150g) in DCM (10ml) was treated with 6-chloronaphthylsulphonyl chloride¹ (0.188g) and pyridine (0.058ml) and stirred at room temperature for 72h. The mixture was washed with water and concentrated under reduced pressure to yield an oil which was purified by BiotageTM chromatography (eluting with cyclohexane:ethyl acetate 2:1) to give the title compounds [(1) – 0.067g and (2) – 0.060g], both as white solids.

- 35 (1) Mass spectrum: Found: MH^+ 453

(2) Mass spectrum: Found: MH^+ 453

*Intermediate 41 \equiv Intermediate 27

Using Intermediates 41 and 42 and the synthetic procedure described for Intermediate 52, the following compounds were similarly prepared:

40

Intermediate 43

tert-Butyl(2R)-2-[(3R)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl]propanoate

Mass spectrum: Found: MH⁺ 467

5

Intermediate 44

tert-Butyl(2R)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl]propanoate

Mass spectrum: Found: MH⁺ 467

10

Intermediate 45

tert-Butyl (2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](2-oxobutyl)amino]-2-oxopyrrolidin-1-yl]propanoate

A solution of *tert*-butyl (2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoate (0.07g) in THF (2ml) was cooled to -78°C under nitrogen, and treated with lithium bis(trimethylsilyl) amide (1.0M solution in THF; 0.186ml), followed by 1-bromo-2-butanone (0.08ml). The resultant solution was allowed to reach room temperature and stirred for a further 72h. Methanol (1ml) was added and the resultant solution concentrated under reduced pressure. The residue was purified using SPE (silica, eluting with cyclohexane:ethyl acetate 10:1, 5:1, 3:1, 2:1, 1:1, 1:2, 1:3, 1:5, ethyl acetate and methanol:ethyl acetate 1:9) to give the title compound (0.07g) as a gum.

Mass spectrum: Found: MH⁺ 523

Similarly prepared using other commercially available alkyl halides, were:

25 Intermediate 46

tert-Butyl (2S)-2-[(3S)-3-[(2-amino-2-oxoethyl)[(6-chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoate

Mass spectrum: Found: MH⁺ 510

30 Intermediate 47

tert-Butyl (2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](2-methoxy-2-oxoethyl)amino]-2-oxopyrrolidin-1-yl]propanoate

Mass spectrum: Found: MH⁺ 525

35 Intermediate 48

(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](2-oxobutyl)amino]-2-oxopyrrolidin-1-yl]propanoic acid

tert-Butyl (2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](2-oxobutyl)amino]-2-oxopyrrolidin-1-yl]propanoate (0.07g) was dissolved in DCM (2ml), and trifluoroacetic acid (2ml) was added.

40 The mixture was stirred at room temperature for 1.5h and then partitioned between water

and DCM. The organic layer was separated, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (0.063g) as an orange gum. Mass spectrum: Found: MH^+ 467

Using similar chemistry, the following were prepared:

5

Intermediate 49

(2S)-2-((3S)-3-((2-Amino-2-oxoethyl)((6-chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoic acid

Using Intermediate 46 and similar chemistry to that described for Intermediate 48, the title compound was prepared.

10

Mass spectrum: Found: MH^+ 454

Intermediate 50

(2S)-2-((3S)-3-(((6-Chloro-2-naphthyl)sulfonyl)(2-methoxy-2-oxoethyl)amino)-2-oxopyrrolidin-1-yl)propanoic acid

15

Using Intermediate 47 and similar chemistry to that described for Intermediate 48, the title compound was prepared.

Mass spectrum: Found: MH^+ 469

20 Intermediate 51

7-(((3S)-1-((1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl)-2-oxopyrrolidin-3-yl)amino)sulfonyl]-2-naphthyl benzoate

The title compound was prepared using Intermediate 23, 7-(chlorosulfonyl)-2-naphthyl benzoate, and the synthetic procedure described for Intermediate 25.

25 Mass spectrum: Found: MH^+ 446

Intermediate 52

tert-Butyl (2S)-2-((3S)-3-(((6-chloro-2-naphthyl)sulfonyl)(methyl)amino)-2-oxopyrrolidin-1-yl)propanoate

30 A solution of *tert*-butyl (2S)-2-((3S)-3-(((6-chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoate (0.1g) in THF (5ml) was cooled to -78°C under nitrogen, and treated with lithium bis(trimethylsilyl) amide (1.0M solution in THF; 0.23ml), followed by methyl tosylate (0.206g). The resultant solution was allowed to reach room temperature and stirred for a further 16h. The mixture was quenched with sodium acetate (0.074g), stirred for 1h and

35 partitioned between water and ethyl acetate. The separated organic layer was washed with water, dried (over magnesium sulphate), and concentrated under reduced pressure. The residue was purified using SPE (silica, eluting with cyclohexane:ethyl acetate 10:1, 8:1, 5:1, 3:1, 2:1, 1:1) to give the title compound (0.101g) as a colourless gum.

Mass spectrum: Found: MH^+ 467

40

Intermediate 53

(2S)-2-((3S)-3-((6-chloro-2-naphthyl)sulfonyl)(methyl)amino)-2-oxopyrrolidin-1-yl}propanoic acid

- 5 *tert*-Butyl (2S)-2-((3S)-3-((6-chloro-2-naphthyl)sulfonyl)(methyl)amino)-2-oxopyrrolidin-1-yl}propanoate (0.1g) was dissolved in DCM (2ml), and trifluoroacetic acid (2ml) was added. The mixture was stirred at room temperature for 1.5h and then partitioned between water and DCM. The organic layer was separated, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (0.09g) as an colourless gum.
- 10 Mass spectrum: Found: MH^+ 411

Intermediate 54

(2R)-2-((3S)-3-((6-chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl}propanoic acid

- 15 Using Intermediate 42 and the procedure described for Intermediate 53, the title compound was similarly prepared.
- Mass spectrum: Found: MH^+ 397

Intermediate 55

(2R)-2-((3S)-3-((6-chloro-2-naphthyl)sulfonyl)(methyl)amino)-2-oxopyrrolidin-1-yl}propanoic acid

- 20 Using Intermediate 44 and the procedure described for Intermediate 53, the title compound was similarly prepared.
- Mass spectrum: Found: MH^+ 411

25 Intermediate 56

(2R)-2-((3R)-3-((6-chloro-2-naphthyl)sulfonyl)(methyl)amino)-2-oxopyrrolidin-1-yl}propanoic acid

- Using Intermediate 43 and the procedure described for Intermediate 53, the title compound was similarly prepared.
- 30 Mass spectrum: Found: MH^+ 411

Intermediate 57

5-Chlorothieno[2,3-b]pyridine-2-sulfonyl chloride

- 35 *n*-Butyl lithium (1.6M in hexanes, 0.37ml) was added to a cooled (-78°C) solution of 5-chlorothieno[2,3-b]pyridine* (0.100g) in anhydrous THF (5ml) over 15min. The reaction was stirred for a further 5min, warmed to -45°C and stirred for 40min. The mixture was cooled to -70°C and sulphur dioxide gas was bubbled into the vessel over 10min. The reaction was allowed to reach room temperature over 45min, and then concentrated under reduced pressure. The residue was dissolved in anhydrous DCM (5ml), treated with N-
- 40 chlorosuccinimide (0.097g) and stirred at room temperature for 75min. The solution was

filtered, and the filtrate concentrated under reduced pressure to give the title compound (0.198g) as a yellow solid.

Mass Spectrum: Found: MH^+ 277 for dimethylamine quenched mass spectrum sample

*Klemm. L.H. et.al., J. Heterocycl. Chem. (1968), 5(6), 773-8.

5

Intermediate 58

tert-Butyl 3-(benzoylamino)piperidine-1-carboxylate

A solution of benzoic acid (0.123g) in DMF (5ml) was treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.231g), HOBt (0.163g) and
10 triethylamine (0.56ml) and stirred at room temperature for 1h. A solution of 3-amino-1-N-Boc-piperidine (0.3g) in DMF (1ml) was then added and stirring continued for 18h. The solution was concentrated under reduced pressure to give an oil which was partitioned between ethyl acetate and water. The separated organic extracts were washed with water, hydrochloric acid (2N), saturated sodium bicarbonate solution and brine, dried (over
15 magnesium sulphate) and concentrated under reduced pressure to give the title compound (0.120g) as a yellow solid.

Mass spectrum: Found: MH^+ 305

Intermediate 59

N-Piperidin-3-ylbenzamide

A solution of *tert*-butyl 3-(benzoylamino)piperidine-1-carboxylate (0.120g) in DCM (5ml) was treated with trifluoroacetic acid (5ml) and stirred at room temperature for 6h. The mixture was concentrated under reduced pressure to give a yellow oil which following neutralisation with aqueous ammonia solution, was purified using SPE (silica, eluting with methanol and
25 5% aqueous ammonia in methanol) to give the title compound (0.085g) as an off-white solid.
 1H NMR (D_4MeOH): δ 7.82(2H, br.d), 7.53(1H, tt), 7.45(2H, t), 4.27(1H, tt), 3.50(1H, br.dd), 3.34(1H, br.dt), 2.96(2H, m), 2.08(2H, m), 1.90-1.68(2H, m) ppm.

Intermediate 60

tert-Butyl (2S)-2-((3S)-3-[[6-chloro-2-naphthyl)sulfonyl](2-furylmethyl)amino]-2-oxopyrrolidin-1-yl)propanoate

A solution of *tert*-butyl (2S)-2-((3S)-3-[[6-chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoate (0.07g) in THF (0.5ml) was treated with diisopropyl azodicarboxylate (0.06ml), 3-furfuryl alcohol (0.030g) and tributylphosphine (0.075ml) and shaken at room
35 temperature for 18h. The mixture was concentrated under reduced pressure and the residue purified by BiotageTM chromatography (eluting with cyclohexane:ethyl acetate 3:1) to give the title compound (0.015g) as a colourless gum.

Mass spectrum: Found: MH^+ 533

Using similar chemistry, the following was prepared:

40

Intermediate 61

tert-Butyl (2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](1,3-thiazol-2-ylmethyl)amino]-2-oxopyrrolidin-1-yl]propanoate

Mass spectrum: Found: MH^+ 550

5

Intermediate 62

(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](1,3-thiazol-2-ylmethyl)amino]-2-oxopyrrolidin-1-yl]propanoic acid

A solution of *tert*-butyl (2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](1,3-thiazol-2-ylmethyl)amino]-2-oxopyrrolidin-1-yl]propanoate (0.03g) in DCM (1ml) was treated with trifluoroacetic acid (1ml) and stirred at room temperature for 1h. The solution was then concentrated under reduced pressure to give the title compound (0.019g) as a colourless solid.

Mass spectrum: Found: MH^+ 494

15 Using Intermediate 60 and similar chemistry to that described for Intermediate 62, the following was prepared:

Intermediate 63

(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](2-furylmethyl)amino]-2-oxopyrrolidin-1-yl]propanoic acid mixture with (2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoic acid (56:44)

Mass spectrum: Found: MH^+ 478

Intermediate 64

25 *tert*-Butyl 5-chloro-2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]amino)sulfonyl]-1H-indole-1-carboxylate

1-*tert*-Butoxycarbonyl-5-chloroindole (0.1g) was dissolved in anhydrous THF (2ml) under nitrogen and cooled to -78°C . *n*-Butyllithium (1.6M in hexanes, 0.273ml) was added dropwise over 10min. After stirring at -78°C for 45min, sulphur dioxide gas was bubbled through the reaction for 5min. The reaction mixture was allowed to reach room temperature over 2h and concentrated under reduced pressure to give an off-white solid. The solid was re-suspended in anhydrous DCM (2ml) and treated with N-chlorosuccinimide (0.0584g). The mixture was then stirred for 1h at room temperature and any remaining white solid removed by filtration. Half of this filtrate was treated with pyridine (0.017ml) and Intermediate 87 (0.022g). The reaction mixture was stirred at 40°C for 5h and then 72h at 30°C in a sealed vessel. The reaction mixture was washed with water, the organic phase separated and dried (over magnesium sulphate), and concentrated under a stream of nitrogen to give a residue which was purified by mass directed preparative h. p.l.c. to give the title compound (0.011g) as a colourless glass.

40 Mass spectrum: Found: MH^+ 555

Intermediate 65

N-((3S)-1-[(1S)-1-Methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethanesulfonamide

- 5 2-Chloroethanesulfonyl chloride (0.284ml) was added dropwise to a mixture of Intermediate 87 (0.436g) and N,N-di-isopropylethylamine (0.938ml) in dry acetonitrile (6ml) at 0°C over 2min. The mixture was allowed to reach room temperature and stirred for 3 days, after which the reaction was quenched with water and concentrated under reduced pressure to give a brown residue. This residue was partitioned between ethyl acetate and water. The combined
10 organic extracts were dried (over magnesium sulphate) and concentrated under reduced pressure to give a brown foam which was purified by SPE (silica, eluting with ethyl acetate:cyclohexane 1:1, ethyl acetate and then ethyl acetate:methanol 19:1) to give the title compound (0.227g) as a clear film.

Mass Spectrum: Found: MH⁺ 332

15

Intermediate 66

(3S)-3-[(6-Chloro-1,3-benzothiazol-2-yl)thio]amino-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one

- N-Chlorosuccinimide (0.37g) was added to 4-chloro-2-mercaptobenzothiazole (0.5g) in DCM
20 (15ml) under nitrogen, and stirred at room temperature for 3h. A solution of Intermediate 87 (0.569g) and triethylamine (1.04ml) in anhydrous DCM (5ml) were added and the resulting mixture stirred at room temperature under nitrogen for 2h. The solution was filtered and the filtrate was diluted with DCM. The organic solution was washed with water and brine, dried
25 (over magnesium sulphate) and concentrated under reduced pressure. The residue was purified by SPE (silica, eluting with cyclohexane: ethyl acetate 1:1 increasing polarity to ethyl acetate:methanol 19:1) to give the title compound (0.3g) as a white solid.

Mass spectrum: Found: MH⁺ 441

Intermediate 67

- 30 *tert*-Butyl (2S)-2-((3S)-3-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoate

- A solution of *tert*-butyl (2S)-2-[(3S)-3-amino-2-oxopyrrolidin-1-yl]propanoate (0.337g) in acetonitrile (20ml) was treated with triethylamine (0.41ml) and 5'-chloro-2,2'-bithiophene-5-sulfonyl chloride² (0.372g) and stirred at room temperature for 17h. The mixture was
35 concentrated under reduced pressure and the residue purified using SPE (aminopropyl, eluting with methanol) to give the title compound (0.651g) as a brown oil.

Mass spectrum: Found: MH⁺ 491

Using similar chemistry and Intermediate 9, the following were prepared:

- 40 Intermediate 68

tert-Butyl (2S)-2-[(3S)-3-[(E)-2-(4-chlorophenyl)ethenyl]sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoate

Mass spectrum: Found: MH^+ 429

5 Intermediate 69

tert-Butyl (2S)-2-[(3S)-3-[(6-chloro-1-benzothien-2-yl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoate

Mass spectrum: Found: MH^+ 459

10 Intermediate 70

tert-Butyl (2S)-2-[(3S)-3-[(5-chloro-1-benzothien-2-yl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoate

Mass spectrum: Found: MH^+ 459

15 Intermediate 71

tert-Butyl (2S)-2-[(3S)-3-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl](2-oxobutyl)amino]-2-oxopyrrolidin-1-yl]propanoate

Using Intermediate 67, and the synthetic procedure described for Intermediate 45, the title compound was similarly prepared.

20 Mass spectrum: Found: MH^+ 561

Intermediate 72

tert-Butyl (2S)-2-[(3S)-3-[(E)-2-(4-chlorophenyl)ethenyl]sulfonyl](2-oxobutyl)amino]-2-oxopyrrolidin-1-yl]propanoate

25 Using Intermediate 68, and the synthetic procedure described for Intermediate 45, the title compound was similarly prepared.

Mass spectrum: Found: MH^+ 499

Intermediate 73

30 tert-Butyl (2S)-2-[(3S)-3-[(6-chloro-1-benzothien-2-yl)sulfonyl](2-oxobutyl)amino]-2-oxopyrrolidin-1-yl]propanoate

Using Intermediate 69, and the synthetic procedure described for Intermediate 45, the title compound was similarly prepared.

Mass spectrum: Found: MH^+ 529

35

Intermediate 74

tert-Butyl (2S)-2-[(3S)-3-[(5-chloro-1-benzothien-2-yl)sulfonyl](2-oxobutyl)amino]-2-oxopyrrolidin-1-yl]propanoate

40 Using Intermediate 70, and the synthetic procedure described for Intermediate 45, the title compound was similarly prepared.

Mass spectrum: Found: MH^+ 529

Intermediate 75

tert-Butyl (2S)-2-[(3S)-3-{(2-amino-2-oxoethyl)[(E)-2-(4-chlorophenyl)ethenyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]propanoate

Using Intermediate 68, and the synthetic procedure described for Intermediate 45, the title compound was similarly prepared.

Mass spectrum: Found: MH^+ 487

Intermediate 76

tert-Butyl (2S)-2-[(3S)-3-{(2-amino-2-oxoethyl){[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]amino}-2-oxopyrrolidin-1-yl]propanoate

Using Intermediate 67, and the synthetic procedure described for Intermediate 45, the title compound was similarly prepared.

Mass spectrum: Found: MH^+ 548

Intermediate 77

Dimethyl (2R)-2-[(benzyloxy)carbonyl]amino}pentanedioate

Thionyl chloride (30ml) was added to a cooled solution of D-glutamic acid (33.2g) in methanol (250ml) and the mixture subsequently heated under reflux for 16h. On cooling, the mixture was concentrated under reduced pressure and the residue azeotroped with toluene to give a white solid. This was stirred with ethyl acetate, water and potassium hydrogen carbonate at 0°C while benzyl chloroformate (30ml) was added. The mixture was warmed to room temperature and stirred for 5h. The separated organic phase was washed with water, dried (over magnesium sulphate) and concentrated under reduced pressure to provide a yellow oil. This oil was purified using flash column chromatography (silica, eluting with cyclohexane:ethyl acetate 2:1) to give the title compound (22.45g) as an oil.

1H NMR ($CDCl_3$): δ 7.40-7.30(5H, m), 5.50(1H, br.d), 5.10(2H, s), 4.40(1H, m), 3.73(3H, s), 3.64(3H, s), 2.50-2.35(2H, m), 2.30-1.90(2H, 2 x m) ppm.

Intermediate 78

Benzyl (1S)-4-hydroxy-1-(hydroxymethyl)butylcarbamate

A solution of Z-glutamic acid (10g) in THF (50ml) was added portionwise to a stirred solution of lithium aluminium hydride in THF (1M, 100ml) under nitrogen at 0°C, and the resultant mixture stirred at room temperature for 24h. Wet ether was added and the mixture was diluted with water and ethyl acetate. The mixture was filtered through HarboliteTM and the filtrate diluted further with water. The separated organic phase was washed with water, dried (over magnesium sulphate) and concentrated under reduced pressure to give solid which

was purified by flash column chromatography (silica, eluting with ethyl acetate) to give the title compound (2.74g) as a white solid.

¹H NMR (D₆DMSO): δ 7.40-7.30(5H, m), 6.95(1H, br.d), 5.00(2H, s), 4.65(1H, br.t), 4.40(1H, br.t), 3.50-3.20(5H, m), 1.65-1.15(4H, m) ppm.

5

Intermediate 79

Benzyl (1R)-4-hydroxy-1-(hydroxymethyl)butylcarbamate

A solution of dimethyl (2R)-2-[[benzyloxy]carbonyl]amino}pentanedioate (22.4g) in dry THF (74ml) was added dropwise over 1h to a stirred mixture of lithium borohydride (4.5g) in THF (200ml) at room temperature, under nitrogen. Stirring at room temperature was continued for 3 days. The reaction mixture was diluted with brine and water, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (16.5g) as a white solid.

15 ¹H NMR (D₆DMSO): δ 7.41-7.30(5H, m), 7.00(1H, br.d), 5.02(2H, s), 4.65(1H, br.t), 4.40(1H, br.t), 3.50-3.20(5H, m), 1.63-1.20(4H, m) ppm.

Intermediate 80

(2R)-2-[[Benzyloxy]carbonyl]amino}-5-[(methylsulfonyl)oxy]pentyl methanesulfonate

20 A solution of benzyl (1R)-4-hydroxy-1-(hydroxymethyl)butylcarbamate (1.5g) in DCM (60ml) was treated with triethylamine (3.3ml) and stirred at room temperature for 10min. Methanesulphonyl chloride (1.34ml) was then added dropwise and the resultant mixture stirred at 0°C for 75min. Sodium bicarbonate solution was added and the reaction mixture allowed to reach room temperature over 1h. The organic layer was separated, washed with 25 brine, dried (over magnesium sulphate) and concentrated under reduced pressure to give a yellow oil. The oil was purified using BiotageTM chromatography (eluting with hexane:ethyl acetate 1:2, 1:3) to give the title compound (1.924g) as a yellow oil

Mass spectrum: Found: MH⁺ 410

Similarly prepared using Intermediate 80 was:

30

Intermediate 81

(2S)-2-[[Benzyloxy]carbonyl]amino}-5-[(methylsulfonyl)oxy]pentyl methanesulfonate

Mass spectrum: Found: MH⁺ 410

35 Intermediate 82

Benzyl (3R)-piperidin-3-ylcarbamate

Liquid ammonia (ca. 30ml) was added to a solution of (2R)-2-[[benzyloxy]carbonyl]amino}-5-[(methylsulfonyl)oxy]pentyl methanesulfonate (1g) in THF (15ml) at -78°C in a bomb reaction vessel and then the resultant mixture was allowed to reach room temperature. After 40 46h, the solution was concentrated under reduced pressure to give an off-white solid which

was purified using SPE (silica, eluting with methanol, methanol:aqueous ammonia 95:5, 9:1) to give the title compound (0.587g) as an off white solid.

Mass spectrum: Found: MH^+ 235

Similarly prepared using Intermediate 81 was:

5

Intermediate 83

Benzyl (3S)-piperidin-3-ylcarbamate

Mass spectrum: Found: MH^+ 235

10 Intermediate 84

Benzyl (3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate

A solution of (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid (0.408g) in DCM (21ml) was treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.394g), HOBt (0.278g) and triethylamine (0.286ml) and stirred at room temperature for 1h. A solution of benzyl (3S)-piperidin-3-ylcarbamate (0.361g) in DCM (1ml) was then added and stirring continued for 72h. The mixture was partitioned between DCM and water. The separated organic extracts were washed with water and brine, dried (over magnesium sulphate), and concentrated under reduced pressure. The residue was purified using BiotageTM chromatography (eluting with hexane:ethyl acetate 1:7→1:10) to give the title compound (0.268g) as an oil.

Mass spectrum: Found: MH^+ 614

Intermediate 85

25 Benzyl (3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate

Using benzyl (3R)-piperidin-3-ylcarbamate and the procedure described for Intermediate 84, the title compound was prepared.

Mass spectrum: Found: MH^+ 614

30

Intermediate 86

Benzyl (3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-ylcarbamate

(2S)-2-((3S)-3-[(Benzyloxy)carbonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid (84.5g) was dissolved in DMF (2l) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (161g) was added, followed by N,N-diisopropylethylamine (92ml) and morpholine (46ml). The mixture was stirred under nitrogen for 2.5h, and saturated aqueous ammonium chloride was added. The mixture was stirred for 15min then partitioned between water and ethyl acetate. The separated organic phase was washed with lithium chloride (10% by weight), followed by saturated sodium bicarbonate and brine. The organic layer was

dried (over sodium sulphate) and concentrated under reduced pressure to give the title compound (65g) as a yellow solid.

Mass spectrum: Found: MH^+ 376

5 Intermediate 87

(3S)-3-Amino-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one

A mixture of benzyl (3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-ylcarbamate (20g), 10 % palladium on carbon (2g) and ethanol (1.3l) was stirred under an atmosphere of hydrogen for 16h. The reaction mixture was filtered through Celite™ and the
10 filtrate was concentrated under reduced pressure to give the title compound (12.3g) as a pale white oil.

1H NMR (D_4MeOH): δ 5.05(1H, dd), 3.59(9H, m), 3.37(2H, m), 2.42(1H, m), 1.75(1H, m), 1.30(3H, d) ppm.

15 Intermediate 88

6-Chloro-N-((3S)-1-[(1S)-2-[(1R,5S)-3-(tert-butyloxycarbonyl)-7-diazabicyclo[3.3.1]non-3-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Using Example 408 and N-Boc-sarcosine, and the synthetic procedure described for Example 409, the title compound was prepared.

20 Mass spectrum: Found: MH^+ 676

Intermediate 89

tert-Butyl (2S)-2-((3S)-3-[(2-methyl-1,3-thiazol-4-yl)methyl]amino)-2-oxopyrrolidin-1-yl)propanoate

25 A solution of 2-methyl-1,3-thiazole-4-carbaldehyde (0.028g) in DCM (2ml) was treated with Intermediate 9 (0.05g) followed by acetic acid (0.013ml) and tetramethylammonium triacetoxyborohydride (0.116g), and the resultant mixture stirred at room temperature for 66h. The reaction mixture was partitioned between water and DCM. The organic layer was separated, dried (over magnesium sulphate) and concentrated under reduced pressure to
30 give the title compound (0.07g) as an oil.

Mass spectrum: Found: MH^+ 340

Using similar chemistry, the following were prepared:

Intermediate 90

35 tert-Butyl (2S)-2-((3S)-2-oxo-3-[(pyridin-4-ylmethyl)amino]pyrrolidin-1-yl)propanoate

Mass spectrum: Found: MH^+ 320

Intermediate 91

tert-Butyl (2S)-2-((3S)-2-oxo-3-[(pyridin-2-ylmethyl)amino]pyrrolidin-1-yl)propanoate

40 Mass spectrum: Found: MH^+ 320

Intermediate 92

tert-Butyl (2S)-2-((3S)-3-[[[6-chloro-2-naphthyl)sulfonyl]](2-methyl-1,3-thiazol-4-yl)methyl]amino}-2-oxopyrrolidin-1-yl)propanoate

- 5 Using Intermediate 89 and the synthetic procedure described for Intermediate 25, the title compound was similarly prepared.

Mass spectrum: Found: MH^+ 564

Intermediate 93

- 10 tert-Butyl (2S)-2-((3S)-3-[[[6-chloro-2-naphthyl)sulfonyl]](pyridin-4-ylmethyl)amino]-2-oxopyrrolidin-1-yl}propanoate

Using Intermediate 90 and the synthetic procedure described for Intermediate 25, the title compound was similarly prepared.

Mass spectrum: Found: MH^+ 544

15

Intermediate 94

tert-Butyl (2S)-2-((3S)-3-[[[6-chloro-2-naphthyl)sulfonyl]](pyridin-2-ylmethyl)amino]-2-oxopyrrolidin-1-yl}propanoate

Using Intermediate 91 and the synthetic procedure described for Intermediate 25, the title compound was similarly prepared.

20

Mass spectrum: Found: MH^+ 544

Intermediate 95

(2S)-2-((3S)-3-[[[6-Chloro-2-naphthyl)sulfonyl]](2-methyl-1,3-thiazol-4-yl)methyl]amino}-2-oxopyrrolidin-1-yl)propanoic acid

25

Using Intermediate 92 and the synthetic procedure described for Intermediate 13, the title compound was similarly prepared.

Mass spectrum: Found: MH^+ 508

30

Intermediate 96

(2S)-2-((3S)-3-[[[6-Chloro-2-naphthyl)sulfonyl]](pyridin-4-ylmethyl)amino]-2-oxopyrrolidin-1-yl}propanoic acid hydrochloride

Using Intermediate 93 and the synthetic procedure described for Intermediate 13, the title compound was similarly prepared.

35

Mass spectrum: Found: MH^+ 488

Intermediate 97

(2S)-2-((3S)-3-[[[6-Chloro-2-naphthyl)sulfonyl]](pyridin-2-ylmethyl)amino]-2-oxopyrrolidin-1-yl}propanoic acid hydrochloride

Using Intermediate 94 and the synthetic procedure described for Intermediate 13, the title compound was similarly prepared.

Mass spectrum: Found: MH^+ 488

5 Intermediate 98

(3S)-3-[[2-Methoxy-4-(2-polystyrylethoxy)benzyl]amino]-1-[(1S)-1-methyl-2-oxo-2-(1-piperidinyl)ethyl]-2-pyrrolidinone

A solution of (3S)-3-amino-1-[(1S)-1-methyl-2-oxo-2-(1-piperidinyl)ethyl]-2-pyrrolidinone (0.795g) in anhydrous DMF (ca. 8ml) was added to pre-swollen 2-(3-methoxy-4-formylphenoxy)ethoxymethyl polystyrene resin (1.45g) followed by the N,N-diisopropylethylamine (0.58ml) and acetic acid (0.19ml). The mixture was shaken at room temperature for 2h, after which time a solution of tetra *n*-butylammonium borohydride (0.856g) and acetic acid (0.19ml) in anhydrous DMF (ca. 5ml) was added. The mixture was shaken for 20h at room temperature, filtered and washed with DMF, 10% ethanolamine in DMF, DMF, DCM, methanol and diethyl ether. The resultant resin was dried *in vacuo* to give the title compound (1.53g) as pale yellow beads.

IR: ν_{\max} 2890, 2327, 2282, 1749, 1715 and 1643 cm^{-1}

Intermediate 99

20 5-Bromo-N-[2-methoxy-4-(2-polystyrylethoxy)benzyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(1-piperidinyl)ethyl]-2-oxopyrrolidinyl]-2-thiophenesulfonamide

Intermediate 98 pre-swollen with DCM (ca. 15ml) and then filtered, was treated with a solution of 5-bromothiophene-2-sulfonyl chloride (0.85g) in DMF (15ml), followed by N,N-diisopropylethylamine (1.14ml). The mixture was shaken for 20h at room temperature, 25 filtered, washed with DMF, DCM and diethyl ether. The resultant solid was dried *in vacuo* to give the title compound (1.59g) as an orange/brown resin.

0.025g of this resin was treated with trifluoroacetic acid-DCM (1:1, 1ml) and shaken for 2h and filtered. The filtrate was concentrated under a stream of nitrogen to give Example 367 (0.0025g) as an off-white glass.

30 Mass spectrum: Found: MH^+ 465

Intermediate 100

tert-butyl (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl](2-benzyloxy-2-oxoethyl)amino)-2-oxopyrrolidin-1-yl)propanoate

35 To a solution of *tert*-butyl (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoate (1g) in DMF (20ml) was added potassium carbonate (0.92g) and benzyl-2-bromoacetate (0.33g), and the mixture was stirred under nitrogen at room temperature for 72h. The reaction mixture was filtered, concentrated under reduced pressure, and the residue partitioned between water and DCM. The organic layer was

100

isolated, dried (over magnesium sulphate and purified by SPE (silica, cyclohexane:ethyl acetate 2:1) to give the title compound (1.0g) as a white solid.

Mass spectrum: Found: MH^+ 601

5 Intermediate 101

Benzyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)glycinate formate

A mixture of Intermediate 100 (0.5g) was dissolved in DCM (10ml) and cooled to 0°C, using an ice bath. Trifluoroacetic acid (10ml) was added dropwise, and the solution left to warm to room temperature over 2h. The reaction mixture was concentrated under reduced pressure to give a clear residue (0.45g) that was dissolved in DCM (20ml). 1-Hydroxybenzotriazole hydrate (0.34g), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.48g) and (S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (0.39g) were added, and the resultant solution was stirred at room temperature for 0.5h. Triethylamine (0.5ml) was added, and the resultant mixture stirred under nitrogen for 72h. The mixture was washed with water and the aqueous layer re-extracted with DCM. The combined organic layers were dried (over magnesium sulfate), filtered and concentrated under reduced pressure. The residue was purified by mass directed preparative h.p.l.c. to give the title compound (0.18g) as a white solid.

Mass spectrum: Found: MH^+ 681

20

Intermediate 1025-Chloro-1-benzofuran

To a solution of 5-chloro-1-benzofuran-2-carboxylic acid (0.2g) in 1-methyl-2-pyrrolidinone (2ml) was added copper granules (0.2g). The reaction mixture was heated at 250°C for 3.5min in a microwave. The reaction vessel was cooled to room temperature and the mixture combined with four other similar mixtures and the combined mixtures partitioned between water and diethyl ether. The organic layer was washed with water and brine, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (0.65g) as a yellow oil.

30 Gas-chromatography electron-ionisation spectrum: Found: M^+ 152, Rt 5.72min

Intermediate 1035-Chloro-1-benzofuran-2-sulfonyl chloride

n-Butyl lithium (1.6M in hexanes, 0.45ml) was added to a cooled (-78°C) solution of Intermediate 102 (0.11g) in anhydrous THF (5ml) over 5min. The reaction was stirred for a further 5min, warmed to -45°C and stirred for 40min. The mixture was cooled to -70°C and sulphur dioxide gas bubbled into the vessel over 7min. The solution was allowed to warm to room temperature over 45min, and then concentrated under reduced pressure to give a yellow gum. To a suspension of the gum in anhydrous DCM (4ml) was added N-chlorosuccinimide (0.118g) and the mixture stirred at room temperature for 75min. The

40

solution was filtered, and the filtrate concentrated under reduced pressure to give the title compound (0.093g) as a yellow solid.

Mass Spectrum: Found: MH^+ 260 for dimethylamine quenched sample

5 Intermediate 104

2-Chloro-4-ethenylphenol

To a slurry of methyltriphenylphosphonium bromide (0.23g) in dry THF (5ml) under nitrogen at -78°C , *n*-butyl lithium (1.6M in hexanes, 0.37ml) was added dropwise over 2min. The mixture was allowed to warm to 0°C , stirred for 20min, cooled to -78°C and a solution of 3-chloro-4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]benzaldehyde* (0.134g) in dry THF (5ml) added. The reaction mixture was allowed to reach room temperature overnight and quenched with saturated aqueous ammonium chloride. The resultant mixture was extracted with diethyl ether and the combined organic extracts were concentrated under reduced pressure. The residue was purified using SPE (silica, eluting with cyclohexane, followed by 5% to 25% ethyl acetate:cyclohexane) to give the title compound (0.049g) as an oil.

H.p.l.c. (1) Rt 3.26min

*Boukouvalas, J; Maltais, F; Lachance, N., Tetrahedron Lett. (1994), 35(43), 7897-900.

Intermediate 105

20 *tert*-Butyl(2-chloro-4-vinylphenoxy)diphenylsilane

A mixture of Intermediate 104 (0.038g), imidazole (0.042g) and *tert*-butyldiphenylsilyl chloride (0.083ml) was stirred in dry DMF (0.5ml) at room temperature under nitrogen for 20h. The mixture was quenched with water, extracted with diethyl ether, dried (over magnesium sulphate), filtered and concentrated under reduced pressure. The resultant oil was purified using SPE (silica, eluting with cyclohexane followed by 5% to 20% ethyl acetate:cyclohexane) to give the title compound (0.102g) as an oil.

H.p.l.c. (1) Rt 4.71min

Intermediate 106

30 3-[[*tert*-Butyl(dimethyl)silyl]oxy]-4-chlorobenzaldehyde

A mixture of 4-chloro-3-hydroxy-benzaldehyde* (0.354g), 4-N,N-dimethylaminopyridine (0.028g), *tert*-butyldimethylsilyl chloride (0.409g) and triethylamine (0.473ml) in DCM (15ml) was stirred at room temperature under nitrogen for 19h. The mixture was quenched with saturated aqueous sodium bicarbonate and extracted with diethyl ether. The combined organic extracts were concentrated under reduced pressure to give an oil which was purified using SPE (silica, eluting with cyclohexane followed by 10% to 30% ethyl acetate-cyclohexane) to give the title compound (0.42g) as an oil.

H.p.l.c. (1) Rt 4.11min

*Kelley, J; Linn, J; Selway, J. W. T., J. Med. Chem. (1989), 32(8), 1757-63.

Intermediate 1072-Chloro-5-vinylphenol

The title compound was prepared using Intermediate 106, and the synthetic procedure described for Intermediate 104.

5 H.p.l.c. (1) Rt 3.22min

Intermediate 108*tert*-Butyl(2-chloro-5-vinylphenoxy)diphenylsilane

10 The title compound was prepared using Intermediate 107, and the synthetic procedure described for Intermediate 105.

H.p.l.c. (1) Rt 4.68min

Intermediate 109

15 (E)-2-(3-{{*tert*-Butyl(diphenyl)silyl}oxy}-4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

Sulphuryl chloride (0.103ml) was added dropwise to DMF (0.116ml) at 0°C under nitrogen, over 5min. The mixture was allowed to reach room temperature and stirred for 30min. Intermediate 108 (0.293g) in cyclohexane (0.2ml) was added in one portion and the resultant mixture was heated at 90°C for 6h. The cooled mixture was poured onto crushed ice, 20 extracted with diethyl ether, dried (over sodium sulphate) and concentrated under reduced pressure. This crude sulfonyl chloride was treated with Intermediate 87 (0.134g), 4-dimethylaminopyridine (0.0068g), di-isopropylethylamine (0.192ml) in dry DCM (5ml), and after stirring for 3 days at room temperature under nitrogen, the mixture was concentrated under reduced pressure. The resultant solution was washed with water and filtered through 25 a hydrophobic frit. The filtrate was concentrated under reduced pressure, and the remaining oil purified by SPE (silica, eluting with cyclohexane/ethyl acetate 19:1 and then 10:1) followed by mass directed preparative h.p.l.c. to give the title compound (0.0078g) as a colourless gum.

Mass spectrum: Found: MH⁺ 696

30

Intermediate 110Ethyl 2-azido-4-{{1-(*tert*-butoxycarbonyl)propyl}amino}butanoate

To a solution of *tert*-butyl 2-amino-butanoate (0.397g) and ethyl 2-azido-4-bromo-butanoate (0.286g) in acetonitrile (5ml) was added triethylamine (0.347ml). The mixture was heated at 35 50°C for 18h, cooled and evaporated onto silica gel (Merck.7734). The pre-absorbed material was purified by flash column chromatography (Merck. 9385, eluting with cyclohexane:ethyl acetate 6:1) to give the title compound (0.200g) as a mixture of four diastereomers.

Mass spectrum: Found: MH⁺ 315

40

Intermediate 1112-Azido-4-([1-(*tert*-butoxycarbonyl)propyl]amino)butanoic acid

To a solution of Intermediate 110 (0.2g) in THF (3ml) and water (3ml) was added lithium hydroxide (0.038g) and the resultant solution was stirred at room temperature for 18h. The pH of the reaction mixture was adjusted to pH5 with 2N aqueous HCl. The mixture was then concentrated under reduced pressure to give the title compound (0.187g) as a mixture of four diastereomers.

Mass spectrum: Found: MH^+ 287

10 Intermediate 112 and Intermediate 113*tert*-Butyl 2-(3-azido-2-oxopyrrolidin-1-yl)butanoate [Mixture 1 and Mixture 2]

A solution of Intermediate 111 (0.187g), diphenylphosphoryl azide (0.281ml) and triethylamine (0.364ml) in DMF (5ml) was stirred at room temperature for 48h and then concentrated under reduced pressure. The mixture was partitioned between ethyl acetate and water and the organic extract was concentrated under reduced pressure. The resultant oil was purified by flash chromatography (Merck. 9385, eluting with cyclohexane:ethyl acetate 1:1) to give the title diastereomeric compounds as two enantiomeric pairs (0.051g and 0.039g).

Mass Spectrum: Found: MH^+ 269 for both Mixture 1 and Mixture 2

20

Intermediate 114*tert*-Butyl 2-(3-([6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)butanoate [Isomer 1 and Isomer 2]

A mixture of Intermediate 112 [Mixture 1] (0.051g), 10% palladium on carbon (0.01g) and ethanol (5ml) was stirred under an atmosphere of hydrogen for 18h. The reaction mixture was filtered through CeliteTM and the filtrate was concentrated under reduced pressure to give a yellow gum. The gum (0.034g) in DCM (2ml) was treated with 6-chloronaphthylsulphonyl chloride¹ (0.04g) and N,N-diisopropylamine (0.073ml) and stirred at room temperature for 24h. The mixture was washed with water and concentrated under reduced pressure to yield an oil which was partially purified using SPE (silica, eluting with cyclohexane:ethyl acetate 1:1) to give the title compound (0.043g) as a white solid.

Mass spectrum: Found: MH^+ 467

Using Intermediate 113 and similar chemistry to that described above, the following was prepared:

35

Intermediate 115*tert*-Butyl 2-(3-([6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)butanoate [Isomer 3 and Isomer 4]

Mass spectrum: Found: MH^+ 467

40

Intermediate 116

2-(3-{{(6-Chloro-2-naphthyl)sulfonyl}amino}-2-oxopyrrolidin-1-yl)butanoic acid [Isomer 1 and Isomer 2]

Using Intermediate 114 and the synthetic procedure described for Intermediate 13, the title compound was prepared.

H.p.l.c. (1) Rt 3.11min

Intermediate 117

2-(3-{{(6-Chloro-2-naphthyl)sulfonyl}amino}-2-oxopyrrolidin-1-yl)butanoic acid [Isomer 3 and Isomer 4]

Using Intermediate 115 and the synthetic procedure described for Intermediate 13, the title compound was prepared.

H.p.l.c. (1) Rt 3.20min

Intermediate 118

5-Chlorothieno[3,2-b]pyridine-2-sulfonyl chloride

5-Chlorothieno[3,2-b]pyridine* (0.2g) was dissolved in anhydrous THF (10ml) under nitrogen and cooled to -70°C. *n*-Butyllithium (1.6M in hexanes, 0.780ml) was added dropwise over 10min and the mixture stirred for a further 5min. The mixture was warmed to -50°C and stirred for 55min. The reaction was cooled to -70°C, and sulphur dioxide gas was bubbled through the reaction for 10min. The reaction was allowed to warm to room temperature and concentrated under reduced pressure to give a yellow residue which was re-suspended in anhydrous DCM (6ml) and treated with N-chlorosuccinimide (0.189g). The mixture was stirred for 2h at room temperature and any remaining solid removed by filtration. The filtrate was concentrated under reduced pressure to give the title compound (0.153g) as a white solid.

Mass Spectrum: Found: MH⁺ 277 for dimethylamine quenched mass spectrum sample

*Barker. J.N, et.al., J. Chem. Res. (1984), (3), 771-795.

Intermediate 119

(2R)-2-(3-{{(6-Bromo-2-naphthyl)sulfonyl}amino}-2-oxopyrrolidin-1-yl)propanoic acid

Using Intermediate 33 and 6-bromo-2-naphthalenesulfonyl chloride and similar chemistry to that described for Intermediates 35 and 37, the title compound was prepared.

Mass spectrum: Found: MH⁺ 442

Intermediate 120

(2R)-2-(3-{{(5-Chloro-3-methyl-1-benzothien-2-yl)sulfonyl}amino}-2-oxopyrrolidin-1-yl)propanoic acid

Using Intermediate 33 and 5-chloro-3-methylbenzo[b]thiophene-2-sulphonyl chloride and similar chemistry to that described for Intermediates 35 and 37, the title compound was prepared.

Mass spectrum: Found: MH^+ 417

5

Example 1

6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

To a solution of (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid [Intermediate 29] (0.105g) in DCM (10ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.152g), HOBT (0.107g) and triethylamine (0.222ml) and the mixture was stirred at room temperature for 30min. Morpholine (0.07ml) was added and the resultant mixture stirred at room temperature for 16h. The mixture was partitioned between DCM and water. The aqueous layer was re-
10 extracted with DCM and the combined, dried (over magnesium sulphate) organic extracts
15 were concentrated under reduced pressure. The residue was purified using SPE (silica, eluting with cyclohexane:ethyl acetate 5:1, and ethyl acetate) to give the title compound (0.1g) as a white solid.

Mass spectrum: Found: MH^+ 466

20 H.p.l.c. (1) Rt 3.13min

1H NMR (D_4MeOH): δ 8.54(1H, br.s), 8.08-7.96(4H, m), 7.63(1H, dd), 5.00(1H, q), 4.18(1H, dd), 3.69-3.46(9H, m), 3.31-3.29(1H, m), 2.27(1H, m), 1.77(1H, m), 1.26(3H, d) ppm.

The title compound could also be prepared using Intermediate 87 and 6-chloronaphthalene
25 sulphonyl chloride¹, and the chemistry described for the preparation of Example 386 (Route 1).

Using similar chemistry to that described for Example 1, the following were prepared:

Example 2

6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.22min

Example 3

6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate

The title compound was isolated from a crude reaction mixture using mass directed preparative h.p.l.c.

40 Mass spectrum: Found: MH^+ 533

H.p.l.c. (1) Rt 2.64min

Example 4

5 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.1min

Example 5

10 6-Chloro-N-[(3S)-1-((1S)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 549

H.p.l.c. (1) Rt 2.5min

15 Example 6

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate

Mass spectrum: Found: MH^+ 547

H.p.l.c. (1) Rt 2.76min

20

Example 7

1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-3-carboxamide

Mass spectrum: Found: MH^+ 507

25 H.p.l.c. (1) Rt 3.06min

Example 8

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(3-[(trifluoromethyl)sulfonyl]amino)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

30 Mass spectrum: Found: MH^+ 612

H.p.l.c. (1) Rt 3.59min

Example 9

35 1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-2-carboxamide

Mass spectrum: Found: MH^+ 507

H.p.l.c. (1) Rt 3.16min

Example 10

1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidine-4-carboxamide

Mass spectrum: Found: MH^+ 507

H.p.l.c. (1) Rt 3.04min

5

Example 11

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperazin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide trifluoroacetate

tert-Butyl 4-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-

10 yl]propanoyl]piperazine-1-carboxylate was prepared using the generic method as described for Example 1. The title compound was prepared using the synthetic procedure as described for Intermediate 13.

Mass spectrum: Found: MH^+ 465

H.p.l.c. (1) Rt 2.48min

15

Example 12

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(5-oxo-1,4-diazepan-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 493

20 H.p.l.c. (1) Rt 2.74min

Example 13

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

25 Mass spectrum: Found: MH^+ 507

H.p.l.c. (1) Rt 2.81min

Example 14

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-{2-[(4-methylpiperazin-1-yl)methyl]pyrrolidin-1-yl}-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

30 Mass spectrum: Found: MH^+ 562

H.p.l.c. (1) Rt 2.53min

Example 15

35 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-[2-(morpholin-4-ylmethyl)pyrrolidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

Mass spectrum: Found: MH^+ 549

H.p.l.c. (1) Rt 2.56min

40 Example 16

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 450

H.p.l.c. (1) Rt 3.0min

5

Example 17

6-Chloro-N-((3S)-1-((1S)-2-(2,6-dimethylmorpholin-4-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 494

10 H.p.l.c. (1) Rt 3.16min

Example 18

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

15 Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 2.93min

Example 19

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-(3-methylmorpholin-4-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

20 Mass spectrum: Found: MH^+ 480

H.p.l.c. (1) Rt 3.23min

Example 20

25 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide [Isomer 1]

Mass spectrum: Found: MH^+ 561

H.p.l.c. (1) Rt 2.73min

30 Example 21

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide [Isomer 2]

Mass spectrum: Found: MH^+ 561

H.p.l.c. (1) Rt 2.74min

35

Example 22

Methyl 1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoate

Mass spectrum: Found: MH^+ 522

40 H.p.l.c. (1) Rt 3.57min

Example 23

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[3-(pyrrolidin-1-ylcarbonyl)morpholin-4-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

5 Mass spectrum: Found: MH^+ 563

H.p.l.c. (1) Rt 3.08min

Example 24

6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-{2-[(methylsulfonyl)methyl]morpholin-4-yl}-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

10 Mass spectrum: Found: MH^+ 558

H.p.l.c. (1) Rt 3.17min

Example 25

15 6-Chloro-N-((3S)-1-((1S)-2-[2-(methoxymethyl)morpholin-4-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 510

H.p.l.c. (1) Rt 3.02min

20 Example 26 and Example 27

4-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]-N-methylmorpholine-2-carboxamide [Isomer 1 and Isomer 2]

Isomer 1

Mass spectrum: Found: MH^+ 523

25 H.p.l.c. (1) Rt 2.93min

Isomer 2

Mass spectrum: Found: MH^+ 523

H.p.l.c. (1) Rt 2.96min

30 Example 28

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylcarbonyl)morpholin-4-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 563

H.p.l.c. (1) Rt 3.04min

35

Example 29

4-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]-N,N-dimethylmorpholine-2-carboxamide

Mass spectrum: Found: MH^+ 537

40 H.p.l.c. (1) Rt 2.96min

Example 30 Example 31 and Example 32

4-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]-N-(2-hydroxypropyl)morpholine-2-carboxamide [Isomer 1, Isomer 2 and Isomer 3]

5 Isomer 1

Mass spectrum: Found: MH^+ 567

H.p.l.c. (1) Rt 2.92min

Isomer 2

Mass spectrum: Found: MH^+ 567

10 H.p.l.c. (1) Rt 2.91min

Isomer 3

Mass spectrum: Found: MH^+ 567

H.p.l.c. (1) Rt 2.92min

15 Example 33

4-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]-N,N-diisopropylmorpholine-2-carboxamide

Mass spectrum: Found: MH^+ 593

H.p.l.c. (1) Rt 3.4min

20

Example 34

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[2-(piperidin-1-ylcarbonyl)morpholin-4-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 577

25 H.p.l.c. (1) Rt 3.21min

Example 35

6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-{2-[(methylamino)methyl]morpholin-4-yl}-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

30 Mass spectrum: Found: MH^+ 509

H.p.l.c. (1) Rt 2.58min

Example 36

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)morpholin-4-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate

35 Mass spectrum: Found: MH^+ 549

H.p.l.c. (1) Rt 2.58min

Example 37

6-Chloro-N-[(3S)-1-[(1S)-2-(2-[(2-hydroxypropyl)amino]methyl)morpholin-4-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

Mass spectrum: Found: MH^+ 553

H.p.l.c. (1) Rt 2.55min

5

Example 38 and Example 39

6-Chloro-N-[(3S)-1-[(1S)-2-{2-[(dimethylamino)methyl]morpholin-4-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate [Isomer 1 and Isomer 2]

Isomer 1

10 Mass spectrum: Found: MH^+ 523

H.p.l.c. (1) Rt 2.54min

Isomer 2

Mass spectrum: Found: MH^+ 523

H.p.l.c. (1) Rt 2.55min

15

Example 40

6-Chloro-N-[(3S)-1-[(1S)-2-{2-[(diisopropylamino)methyl]morpholin-4-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

Mass spectrum: Found: MH^+ 579

20 H.p.l.c. (1) Rt 2.67min

Example 41

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(piperidin-1-ylmethyl)morpholin-4-yl]ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

25 Mass spectrum: Found: MH^+ 563

H.p.l.c. (1) Rt 2.62min

Example 42 and Example 43

30 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide [Isomer 1 and Isomer 2]

Isomer 1

Mass spectrum: Found: MH^+ 528

H.p.l.c. (1) Rt 2.78min

Isomer 2

35 Mass spectrum: Found: MH^+ 528

H.p.l.c. (1) Rt 2.81min

Example 44

40 6-Chloro-N-[(3S)-1-[(1S)-2-(3,3-difluoropiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 500

H.p.l.c. (1) Rt 3.34min

Example 45

5 6-Chloro-N-((3S)-1-((1S)-2-(4,4-difluoropiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 500

H.p.l.c. (1) Rt 3.33min

10 Example 46

N-((3S)-1-((1S)-2-Azetidin-1-yl-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 436

H.p.l.c. (1) Rt 2.99min

15

Example 47

6-Chloro-N-((3S)-1-((1S)-2-(3-hydroxyazetidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 452

20 H.p.l.c. (1) Rt 2.99min

Example 48

6-Chloro-N-((3S)-1-((1S)-2-((2R,6S)-2,6-dimethylmorpholin-4-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

25 Mass spectrum: Found: MH^+ 494

H.p.l.c. (1) Rt 3.15min

Example 49

6-Chloro-N-((3S)-1-((1S)-2-(3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

30 Mass spectrum: Found: MH^+ 513

H.p.l.c. (1) Rt 2.66min

Example 50

35 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 2.93min

40 Example 51

N-((3S)-1-[(1S)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 476

H.p.l.c. (1) Rt 3.17min

5

Example 52

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

Mass spectrum: Found: MH^+ 527

10 H.p.l.c. (1) Rt 2.67min

Example 53

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

15 Mass spectrum: Found: MH^+ 527

H.p.l.c. (1) Rt 2.66min

Example 54

6-Chloro-N-[(1S)-1-methyl-2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

20

Using Intermediate 38, and the synthetic procedure described for Example 1, the title compound was prepared.

Mass spectrum: Found: MH^+ 479

H.p.l.c. (1) Rt 2.93min

25 Using similar chemistry, the following was prepared:

Example 55

N-[(1S)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide

30 Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 2.93min

Example 56

N-[(3S)-1-[(1S)-2-(2-Azabicyclo[2.2.2]oct-2-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide

35

Mass spectrum: Found: MH^+ 490

H.p.l.c. (1) Rt 3.28min

Example 57

6-Chloro-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Using Intermediate 31, and the synthetic procedure described for Example 1, the title compound was prepared.

5 Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.28min

Using similar chemistry, the following were prepared:

Example 58

10 6-Chloro-N-[(3R)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 466

H.p.l.c. (1) Rt 2.96min

15 Example 59

6-Chloro-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 450

H.p.l.c. (1) Rt 3.12min

20

Example 60

6-Chloro-N-[(3R)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 478

25 H.p.l.c. (1) Rt 3.38min

Example 61

6-Chloro-N-[(3R)-1-[(1S)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

30 Mass spectrum: Found: MH^+ 549

H.p.l.c. (1) Rt 2.67min

Example 62

5'-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide

35 bithiophene-5-sulfonamide

tert-Butyl (2S)-2-[(3S)-3-[[[5'-chloro-2,2'-bithien-5-yl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoate (0.217g) was dissolved in DCM (2ml) and treated with trifluoroacetic acid (2ml) and stirred at room temperature for 2h. The mixture was then concentrated under reduced pressure to give an oil which was subsequently dissolved in DCM (5ml) and treated

40 with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.256g), HOBt (0.184g)

and triethylamine (0.375ml). After the solution had been stirred at room temperature for 30min, morpholine (0.117ml) was added and the resultant mixture stirred for a further 20h. The mixture was concentrated under reduced pressure and the residue partitioned between DCM and water. The organic component was washed with water and brine, and
5 concentrated under reduced pressure. The residue was purified using SPE (silica, eluting with cyclohexane; cyclohexane:ethyl acetate 4:1, 1:1, 1:4; ethyl acetate; methanol:ethyl acetate 1:10; methanol) to give the title compound (0.078g) as a white solid.

Mass spectrum: Found: MH^+ 504

H.p.l.c. (1) Rt 3.17min

10 1H NMR (D_4MeOH): δ 7.61(1H, d), 7.23(1H, d), 7.22(1H, d), 7.03(1H, d), 5.04(1H, q), 4.21(1H, dd), 3.69-3.46(9H, m), 3.39-3.35(1H, m), 2.39(1H, m), 1.86(1H, m), 1.30(3H, d) ppm.

Example 63

15 5'-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-((2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide

Using Intermediate 71 and the synthetic procedure described for Example 62, the title compound was prepared.

Mass spectrum: Found: MH^+ 641

20 H.p.l.c. (1) Rt 2.98min

Example 64

(E)-2-(4-Chlorophenyl)-N-((3S)-1-((1S)-1-methyl-2-oxo-2-((2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)ethenesulfonamide formate

25 Using Intermediate 72 and the synthetic procedure described for Example 62, the title compound was prepared.

Mass spectrum: Found: MH^+ 579

H.p.l.c. (1) Rt 2.75min

30 Example 65

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-((2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide

Using Intermediate 73 and the synthetic procedure described for Example 62, the title compound was prepared.

35 Mass spectrum: Found: MH^+ 609

H.p.l.c. (1) Rt 2.77min

Example 66

40 5-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-((2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide

Using Intermediate 74 and the synthetic procedure described for Example 62, the title compound was prepared.

Mass spectrum: Found: MH^+ 609

H.p.l.c. (1) Rt 2.77min

5

Example 67

5'-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-((2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide

tert-Butyl (2S)-2-((3S)-3-((5'-chloro-2,2'-bithien-5-yl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoate (0.217g) was dissolved in DCM (2ml) and treated with trifluoroacetic acid (2ml) and stirred at room temperature for 2h. The mixture was then concentrated under reduced pressure to give an oil which was subsequently dissolved in DCM (5ml) and treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.256g), HOBT (0.184g) and triethylamine (0.375ml). After the solution had been stirred at room temperature for 15 30min, (S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (0.219ml) was added and the resultant mixture stirred for a further 20h. The mixture was concentrated under reduced pressure and the residue partitioned between DCM and water. The organic component was washed with water and brine, and concentrated under reduced pressure. The residue was purified using SPE (silica, eluting with cyclohexane; cyclohexane:ethyl acetate 4:1, 1:1, 1:4; ethyl acetate; 20 methanol:ethyl acetate 1:10; methanol) to give the title compound (0.042g) as a white solid.

Mass spectrum: Found: MH^+ 571

H.p.l.c. (1) Rt 2.77min

Example 68

25 (E)-2-(4-Chlorophenyl)-N-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)ethanesulfonamide

Using Intermediate 68 and the synthetic procedure described for Example 62, the title compound was prepared.

Mass spectrum: Found: MH^+ 442

30 H.p.l.c. (1) Rt 2.86min

1H NMR ($CDCl_3$): δ 7.46(1H, d), 7.44(2H, d), 7.38(2H, d), 6.89(1H, d), 5.35(1H, br.d), 5.05(1H, q), 4.00(1H, m), 3.69-3.48(9H, m), 3.35(1H, m), 2.62(1H, m), 2.06(1H, m), 1.33(3H, d) ppm.

35 Example 69

N2-((E)-2-(4-Chlorophenyl)ethenyl)sulfonyl-N2-((3S)-1-((1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl)-2-oxopyrrolidin-3-yl)glycinamide

Using Intermediate 75 and the synthetic procedure described for Example 62, the title compound was prepared.

40 Mass spectrum: Found: MH^+ 499

H.p.l.c. (1) Rt 2.81min

Example 70

5 (E)-2-(4-Chlorophenyl)-N-((3S)-1-((1S)-1-methyl-2-oxo-2-((2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)ethenesulfonamide

Using Intermediate 68 and the synthetic procedure described for Example 67, the title compound was prepared.

Mass spectrum: Found: MH^+ 509

H.p.l.c. (1) Rt 2.5min

10

Example 71

N2-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinamide

15 Using Intermediate 76 and the synthetic procedure described for Example 62, the title compound was prepared.

Mass spectrum: Found: MH^+ 561

H.p.l.c. (1) Rt 2.96min

Example 72

20 5'-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide

Using Example 62 and the synthetic procedure described for Example 293, the title compound was prepared.

Mass spectrum: Found: MH^+ 543

25 H.p.l.c. (1) Rt 3.34min

Using similar chemistry, the following were prepared:

Example 73

30 Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinate

Mass spectrum: Found: MH^+ 576

H.p.l.c. (1) Rt 3.34min

Example 74

35 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide

Mass spectrum: Found: MH^+ 574

H.p.l.c. (1) Rt 3.4min

40 Example 75

N-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl]-2-oxoethyl}-2-oxopyrrolidin-3-yl}glycine

Using standard alkaline hydrolysis conditions, the title compound was prepared from Example 73.

- 5 Mass spectrum: Found: MH^+ 562
H.p.l.c. (1) Rt 3.21min

Example 76

(E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl]-2-oxoethyl}-2-oxopyrrolidin-3-yl}ethenesulfonamide

- 10 Using Example 68 and bromoacetonitrile, and the synthetic procedure described for Example 293, the title compound was prepared.
Mass spectrum: Found: MH^+ 481
H.p.l.c. (1) Rt 3.05min
15 Using similar chemistry, the following were prepared:

Example 77

(E)-2-(4-Chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl]-2-oxoethyl}-2-oxopyrrolidin-3-yl}-N-(2-oxobutyl)ethenesulfonamide

- 20 Mass spectrum: Found: MH^+ 512
H.p.l.c. (1) Rt 3.11min

Example 78

Methyl N-[(E)-2-(4-chlorophenyl)ethenyl]sulfonyl}-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl]-2-oxoethyl}-2-oxopyrrolidin-3-yl}glycinate

- 25 Mass spectrum: Found: MH^+ 514
H.p.l.c. (1) Rt 3.05min

Example 79

N-[(E)-2-(4-Chlorophenyl)ethenyl]sulfonyl}-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl]-2-oxoethyl}-2-oxopyrrolidin-3-yl}glycine

- 30 Using standard alkaline hydrolysis conditions, the title compound was prepared from Example 78.
Mass spectrum: Found: MH^+ 500
35 H.p.l.c. (1) Rt 2.9min

Example 80

(E)-2-(4-Chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

tert-Butyl (2S)-2-[(3S)-3-({[(E)-2-(4-chlorophenyl)ethenyl]sulfonyl}amino)-2-oxopyrrolidin-1-yl]propanoate (0.192g) was dissolved in DCM (2ml) and treated with trifluoroacetic acid (2ml) and stirred at room temperature for 2h. The mixture was then concentrated under reduced pressure to give an oil which was subsequently dissolved in DCM (5ml) and treated
5 with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.256g), HOBT (0.184g) and triethylamine (0.375ml). After the solution had been stirred at room temperature for 30min, piperidine (0.133ml) was added and the resultant mixture stirred for a further 20h. The mixture was concentrated under reduced pressure and the residue partitioned between DCM and water. The organic component was washed with water and brine, and
10 concentrated under reduced pressure. The residue was purified using SPE (silica, eluting with cyclohexane; cyclohexane:ethyl acetate 4:1, 1:1, 1:4; ethyl acetate; methanol:ethyl acetate 1:10; methanol) to give the title compound (0.042g) as a white solid.
Mass spectrum: Found: MH^+ 440
H.p.l.c. (1) Rt 3.1min

15

Example 81

Methyl N-{{(E)-2-(4-chlorophenyl)ethenyl}sulfonyl}-N-{{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}glycinate

Using Example 80 and methyl bromoacetate, and the synthetic procedure described for
20 Example 293, the title compound was prepared.

Mass spectrum: Found: MH^+ 512

H.p.l.c. (1) Rt 3.3min

Using similar chemistry, the following was prepared:

25 Example 82

(E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-{{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

Mass spectrum: Found: MH^+ 479

H.p.l.c. (1) Rt 3.31min

30

Example 83

N-{{(E)-2-(4-Chlorophenyl)ethenyl}sulfonyl}-N-{{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}glycine

Using standard alkaline hydrolysis conditions, the title compound was prepared from
35 Example 81.

Mass spectrum: Found: MH^+ 498

H.p.l.c. (1) Rt 3.16min

Example 84

N-{(3S)-1-[(1S)-2-(3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-6-chloronaphthalene-2-sulfonamide

tert-Butyl 1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate (0.6g) was dissolved in DCM (11ml) and trifluoroacetic acid (11ml) was added. The mixture was stirred at room temperature for 2h and then concentrated under reduced pressure. The residue was dissolved in water (5ml) and ammonia solution (0.88%; 1ml) added. The resultant aqueous mixture was extracted with DCM. The combined organic extracts were dried (over magnesium sulphate), filtered and concentrated under reduced pressure to give the title compound (0.38g) as a white foam.

10 Mass spectrum: Found: MH^+ 479

H.p.l.c. (1) Rt 2.71min

Example 85

6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

15 To polymer N-cyclohexylcarbodiimide-N'-propyloxymethyl polystyrene (0.038g) in an AlltechTM tube was added a solution of (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid (0.007g) in DCM (0.9ml) followed by 3-methylpiperidine (0.0025g) in DMF (0.1ml) and N,N-diisopropylethylamine (0.006ml). The mixture was shaken
20 at room temperature for 4 days. The tube was drained, the filtrate collected and the resin washed with DCM. The combined DCM solutions were concentrated under reduced pressure and the residue purified by mass directed preparative h.p.l.c. to give the title compound (0.0023g) as a white solid.

Mass spectrum: Found: MH^+ 478

25 H.p.l.c. (1) Rt 3.25min

Using similar chemistry, the following were prepared:

Example 86

6-Chloro-N-((3S)-1-[(1S)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

30 Mass spectrum: Found: MH^+ 494

H.p.l.c. (1) Rt 2.93min

Example 87

35 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}acetamide

Mass spectrum: Found: MH^+ 521

H.p.l.c. (1) Rt 2.86 and 2.97min (two diastereoisomers)

40 Example 88

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[3-(1H-pyrrol-1-ylmethyl)piperidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 543

H.p.l.c. (1) Rt 3.57min

5

Example 89

6-Chloro-N-((3S)-1-((1S)-2-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 492

10 H.p.l.c. (1) Rt 3.51min

Example 90

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-(2-methylpiperidin-1-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

15 Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.21min

Example 91

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[3-(trifluoromethyl)piperidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

20 Mass spectrum: Found: MH^+ 532

H.p.l.c. (1) Rt 3.52min

Example 92

25 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate

The title compound was isolated from a crude reaction mixture using mass directed preparative h.p.l.c.

Mass spectrum: Found: MH^+ 561

30 H.p.l.c. (1) Rt 2.8min

Example 93

6-Chloro-N-((3S)-1-((1S)-2-(3-methoxypiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

35 Mass spectrum: Found: MH^+ 494

H.p.l.c. (1) Rt 3.04min

Example 94

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-(4-methylpiperidin-1-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

40

Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.43min

Example 95

5 6-Chloro-N-[(3S)-1-[(1S)-2-(3-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 480

H.p.l.c. (1) Rt 3.05min

10 Example 96

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-octahydroquinolin-1(2H)-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 518

H.p.l.c. (1) Rt 3.55min

15

Example 97

6-Chloro-N-[(3S)-1-[(1S)-2-(4-hydroxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 480

20 H.p.l.c. (1) Rt 3.00min

Example 98

6-Chloro-N-[(3S)-1-[(1S)-2-[2-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

25 Mass spectrum: Found: MH^+ 494

H.p.l.c. (1) Rt 3.16min

Example 99

1-[(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoyl]-N,N-diethylpiperidine-3-carboxamide

30 Mass spectrum: Found: MH^+ 563

H.p.l.c. (1) Rt 3.27min

Example 100

35 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-phenylpiperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 530

H.p.l.c. (1) Rt 3.68min

40 Example 101

6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-(3-phenylpiperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 540

H.p.l.c. (1) Rt 3.66min

5

Example 102

6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 561

10 H.p.l.c. (1) Rt 3.32min

Example 103

6-Chloro-N-((3S)-1-[(1S)-2-[4-(dimethylamino)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate

15 Mass spectrum: Found: MH^+ 508

H.p.l.c. (1) Rt 2.64min

Example 104

1-[(2S)-2-((3S)-3-[[6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]-N,N-dimethylprolinamide

20

Mass spectrum: Found: MH^+ 521

H.p.l.c. (1) Rt 3.05min

Example 105

25 N-[1-[(2S)-2-((3S)-3-[[6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]pyrrolidin-3-yl}acetamide

Mass spectrum: Found: MH^+ 507

H.p.l.c. (1) Rt 2.96min

30 Example 106

6-Chloro-N-((3S)-1-[(1S)-2-(3-hydroxypyrrolidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 466

H.p.l.c. (1) Rt 2.95min

35

Example 107

Methyl 1-[(2S)-2-((3S)-3-[[6-chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]-L-prolinate

Mass spectrum: Found: MH^+ 508

40 H.p.l.c. (1) Rt 3.2min

Example 108

6-Chloro-N-((3S)-1-[(1S)-2-(4-methoxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

- 5 Mass spectrum: Found: MH^+ 494
H.p.l.c. (1) Rt 3.17min

Example 109

6-Chloro-N-((3S)-1-[(1S)-2-[4-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

- 10 Mass spectrum: Found: MH^+ 494
H.p.l.c. (1) Rt 3.06min

Example 110

- 15 Methyl 1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-4-carboxylate

Mass spectrum: Found: MH^+ 522
H.p.l.c. (1) Rt 3.32min

20 Example 111

Methyl 1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-3-carboxylate

Mass spectrum: Found: MH^+ 522
H.p.l.c. (1) Rt 3.32min

25

Example 112

2-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]pyrrolidin-2-yl}acetamide

Mass spectrum: Found: MH^+ 507

- 30 H.p.l.c. (1) Rt 2.98min

Example 113

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-4-yl}acetamide

- 35 Mass spectrum: Found: MH^+ 521
H.p.l.c. (1) Rt 2.98min

Example 114

6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-(3-oxopiperazin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

40

Mass spectrum: Found: MH^+ 479

H.p.l.c. (1) Rt 2.94min

Example 115

- 5 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-{3-[(methylamino)methyl]pyrrolidin-1-yl}-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

Mass spectrum: Found: MH^+ 493

H.p.l.c. (1) Rt 2.65min

- 10 Example 116

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 540

H.p.l.c. (1) Rt 3.64min

15

Example 117

N-[(3S)-1-[(1S)-2-(4-Acetyl piperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 506

- 20 H.p.l.c. (1) Rt 3.16min

Example 118

N-[1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]pyrrolidin-3-yl]benzamide

- 25 Mass spectrum: Found: MH^+ 569

H.p.l.c. (1) Rt 3.28min

Example 119

6-Chloro-N-[(3S)-1-[(1S)-2-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

30

Mass spectrum: Found: MH^+ 494

H.p.l.c. (1) Rt 3.24min

Example 120

- 35 Ethyl 1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidine-2-carboxylate

Mass spectrum: Found: MH^+ 536

H.p.l.c. (1) Rt 3.49min

- 40 Example 121

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-(2-methylpyrrolidin-1-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.27min

5

Example 122

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(4-pyrrolidin-1-ylpiperidin-1-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 533

10 H.p.l.c. (1) Rt 2.65min

Example 123

1-((2S)-2-((3S)-3-((6-Chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl]prolinamide

15 Mass spectrum: Found: MH^+ 493

H.p.l.c. (1) Rt 2.95min

Example 124

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-[2-(4-methylpyridin-2-yl)pyrrolidin-1-yl]-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

20

Mass spectrum: Found: MH^+ 541

H.p.l.c. (1) Rt 3.0min

Example 125

6-Chloro-N-((3S)-1-((1S)-2-(3-isopropyltetrahydropyrimidin-1(2H)-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

25

Mass spectrum: Found: MH^+ 507

H.p.l.c. (1) Rt 2.69min

Example 126

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-((2S)-2-(morpholin-4-ylmethyl)pyrrolidin-1-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 549

H.p.l.c. (1) Rt 2.68min

35

Example 127

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-(4,6,7,8-tetrahydro-5H-thieno[3,2-c]azepin-5-yl)ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 532

40 H.p.l.c. (1) Rt 3.54min

Example 128

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(3,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

5 Mass spectrum: Found: MH^+ 502

H.p.l.c. (1) Rt 2.67min

Example 129

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(3,5,6,7-tetrahydro-4H-[1,2,3]triazolo[4,5-b]pyridin-4-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

10

Mass spectrum: Found: MH^+ 503

H.p.l.c. (1) Rt 3.33min

Example 130

15 6-Chloro-N-[(3S)-1-[(1S)-2-(3,4-dihydroquinolin-1(2H)-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 512

H.p.l.c. (1) Rt 3.59min

20 Example 131

6-Chloro-N-[(3S)-1-[(1S)-2-(3,4-dihydroisoquinolin-2(1H)-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 512

H.p.l.c. (1) Rt 3.52min

25

Example 132

6-Chloro-N-[(3S)-1-[(1S)-2-(2,3-dihydro-1H-indol-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 498

30 H.p.l.c. (1) Rt 3.58min

Example 133

6-Chloro-N-[(3S)-1-[(1S)-2-(1,3-dihydro-2H-isoindol-2-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

35 Mass spectrum: Found: MH^+ 498

H.p.l.c. (1) Rt 3.44min

Example 134

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

40

Mass spectrum: Found: MH^+ 526

H.p.l.c. (1) Rt 3.57min

Example 135

- 5 1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]-L-proline

The title compound was prepared by alkaline hydrolysis (lithium hydroxide) of the corresponding methyl ester, Example 107.

Mass spectrum: Found: MH^+ 494

- 10 H.p.l.c. (1) Rt 3.03min

Example 136

1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-3-carboxylic acid

- 15 The title compound was prepared by alkaline hydrolysis (lithium hydroxide) of the corresponding methyl ester, Example 111.

Mass spectrum: Found: MH^+ 508

H.p.l.c. (1) Rt 3.0min

- 20 Example 137

1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-4-carboxylic acid

Mass spectrum: Found: MH^+ 508

H.p.l.c. (1) Rt 3.01min

25

Example 138

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 507

- 30 H.p.l.c. (1) Rt 3.01min

Example 139

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(5-oxo-1,4-diazepan-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

- 35 Mass spectrum: Found: MH^+ 493

H.p.l.c. (1) Rt 2.95min

Example 140

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-thiomorpholin-4-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

40

Mass spectrum: Found: MH^+ 482

H.p.l.c. (1) Rt 3.34min

Example 141

5 6-Chloro-N-[(3S)-1-[(1S)-2-(2,5-dihydro-1H-pyrrol-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 448

H.p.l.c. (1) Rt 3.08min

10 Example 142

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-(2-methylmorpholin-4-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 480

H.p.l.c. (1) Rt 3.17min

15

Example 143

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 493

20 H.p.l.c. (1) Rt 2.64min

Example 144

6-Chloro-N-[(3S)-1-[(1S)-2-(3,6-dihydropyridin-1(2H)-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

25 Mass spectrum: Found: MH^+ 462

H.p.l.c. (1) Rt 3.3min

Example 145

6-Chloro-N-[(3S)-1-[(1S)-2-(1,1-dioxidothiomorpholin-4-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

30 Mass spectrum: Found: MH^+ 514

H.p.l.c. (1) Rt 3.12min

Example 146

35 6-Chloro-N-[(3S)-1-[(1S)-2-(3-hydroxyquinoxalin-1(2H)-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 527

H.p.l.c. (1) Rt 3.23min

40 Example 147

5'-Chloro-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide

To a solution of (3R)-3-amino-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]pyrrolidin-2-one (0.01g) in acetonitrile (1ml) was added triethylamine (0.008ml) and 5'-chloro-2,2'-bithiophene-5-sulfonyl chloride² (0.013g) and the mixture stirred at room temperature for 24h. The mixture was concentrated under reduced pressure and the residue purified by mass directed preparative h.p.l.c. to give the title compound (0.004g) as a white solid.

Mass spectrum: Found: MH⁺ 502

H.p.l.c. (1) Rt 3.43min

10 Using similar chemistry, the following was prepared:

Example 148

(E)-2-(4-Chlorophenyl)-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]ethenesulfonamide

15 Mass spectrum: Found: MH⁺ 440

H.p.l.c. (1) Rt 3.11min

Example 149

tert-Butyl 1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate

20 The title compound was prepared using Intermediate 29 and *tert*-butyl piperidin-3-ylcarbamate, and the synthetic procedure described for Example 1.

Mass spectrum: Found: MH⁺ 579

H.p.l.c. (1) Rt 3.53min

25

Example 150

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}prop-2-ynamide

To a solution of N-[(3S)-1-[(1S)-2-(3-aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloronaphthalene-2-sulfonamide (0.005g) in DMF (0.5ml) were added propiolic acid (0.001g), N,N-diisopropylethylamine (0.0044ml) and o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.004g). The mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was partitioned between DCM and saturated sodium bicarbonate solution and then passed through a hydrophobic frit. The separated organic fraction was concentrated under reduced pressure to give the title compound (0.0064g) as an oil.

35

Mass spectrum: Found: MH⁺ 531

H.p.l.c. (1) Rt 3.42min

Using similar chemistry, the following were prepared:

40

Example 151

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1-methyl-1H-pyrrole-3-carboxamide

Mass spectrum: Found: MH^+ 586

5 H.p.l.c. (1) Rt 3.32min

Example 152

Methyl 4-({1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}amino)-4-oxobutanoate

10 Mass spectrum: Found: MH^+ 593

H.p.l.c. (1) Rt 3.31min

Example 153

4-({1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}amino)-4-oxobutanoic acid

Using standard alkaline hydrolysis conditions, the title compound was prepared from Example 152.

Mass spectrum: Found: MH^+ 579

H.p.l.c. (1) Rt 3.02min

20

Example 154

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1H-1,2,4-triazole-3-carboxamide

Mass spectrum: Found: MH^+ 574

25 H.p.l.c. (1) Rt 3.16min

Example 155

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1-methyl-1H-pyrrole-2-carboxamide

30 Mass spectrum: Found: MH^+ 586

H.p.l.c. (1) Rt 3.33min

Example 156

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}propanamide

Mass spectrum: Found: MH^+ 536

H.p.l.c. (1) Rt 3.18min

Example 157

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1H-pyrazole-3-carboxamide

Mass spectrum: Found: MH^+ 573

H.p.l.c. (1) Rt 3.29min

5

Example 158

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-2-ethylbutanamide

Mass spectrum: Found: MH^+ 577

10 H.p.l.c. (1) Rt 2.71min

Example 159

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}cyclopentanecarboxamide

15 Mass spectrum: Found: MH^+ 575

H.p.l.c. (1) Rt 3.55min

Example 160

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}pentanediamide

20

Mass spectrum: Found: MH^+ 592

H.p.l.c. (1) Rt 3.12min

Example 161

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}pyrazine-2-carboxamide

25

Mass spectrum: Found: MH^+ 584

H.p.l.c. (1) Rt 3.48min

Example 162

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1H-pyrazole-4-carboxamide

30

Mass spectrum: Found: MH^+ 573

H.p.l.c. (1) Rt 3.2min

35

Example 163

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}malonamide

Mass spectrum: Found: MH^+ 564

40 H.p.l.c. (1) Rt 3.11min

Example 164

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-2-methylpropanamide

5 Mass spectrum: Found: MH^+ 549

H.p.l.c. (1) Rt 3.27min

Example 165

N-1-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-N-3,N-3-dimethyl-beta-alaninamide

10

Mass spectrum: Found: MH^+ 578

H.p.l.c. (1) Rt 3.4min

Example 166

15 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}succinamide

Mass spectrum: Found: MH^+ 578

H.p.l.c. (1) Rt 3.09min

20 Example 167

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}prop-2-ynamide

Mass spectrum: Found: MH^+ 531

H.p.l.c. (1) Rt 3.36min

25

Example 168

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1H-pyrrole-2-carboxamide

Mass spectrum: Found: MH^+ 572

30 H.p.l.c. (1) Rt 3.5min

Example 169

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1-methyl-1H-1,2,3-triazole-4-carboxamide

35 Mass spectrum: Found: MH^+ 588

H.p.l.c. (1) Rt 3.4min

Example 170

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-1,3-thiazole-2-carboxamide

40

Mass spectrum: Found: MH^+ 590

H.p.l.c. (1) Rt 3.3min

Example 171

5 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(3-[(trifluoromethyl)sulfonyl]amino)piperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Using triflic anhydride and Example 84, the title compound was prepared as described for Example 150.

Mass spectrum: Found: MH^+ 611

10 H.p.l.c. (1) Rt 3.53min

Example 172

N1-[1-[(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]-N2,N2-dimethylglycinamide

15 Mass spectrum: Found: MH^+ 565

H.p.l.c. (1) Rt 2.63min

Example 173

20 Methyl 3-[(1-[(2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]amino)-3-oxopropanoate

Mass spectrum: Found: MH^+ 579

H.p.l.c. (1) Rt 2.7min

Example 174

25 N-[1-[(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]nicotinamide

Mass spectrum: Found: MH^+ 584

H.p.l.c. (1) Rt 3.17min

30 Example 175 and Example 176

N-[1-[(2S)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]pyridine-2-carboxamide [Isomer 1 and Isomer 2]

Isomer 1

Mass spectrum: Found: MH^+ 584

35 H.p.l.c. (1) Rt 3.48min

Isomer 2

Mass spectrum: Found: MH^+ 584

H.p.l.c. (1) Rt 3.6min

40 Example 177

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-4H-1,2,4-triazole-3-carboxamide

Mass spectrum: Found: MH^+ 574

H.p.l.c. (1) Rt 3.23min

5

Example 178 and Example 179

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-2-ethylbutanamide [Isomer 1 and Isomer 2]

Isomer 1

10 Mass spectrum: Found: MH^+ 578

H.p.l.c. (1) Rt 2.71min

Isomer 2

Mass spectrum: Found: MH^+ 578

H.p.l.c. (1) Rt 3.58min

15

Example 180

N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}prop-2-ynamide

Mass spectrum: Found: MH^+ 531

20 H.p.l.c. (1) Rt 3.36min

Example 181

N-{(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide

25 To a solution of nicotinic acid (0.006g) in DCM (0.5ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.018g), HOBT (0.013g) and triethylamine 0.017ml) and the mixture was stirred at room temperature for 1h. Example 365 (0.015g) was added and the resultant mixture stirred at room temperature for 21h. The mixture was partitioned between DCM and water. The aqueous layer was re-extracted with
30 DCM and the combined, dried (over magnesium sulphate) organic extracts were concentrated under reduced pressure. The residue was purified using SPE (silica, eluting with cyclohexane:ethyl acetate 5:1, 1:1, 1:5, and DCM:methanol 25:1, 15:1, 5:1) to give the title compound (0.01g) as a white solid.

Mass spectrum: Found: MH^+ 584

35 H.p.l.c. (1) Rt 3.24min

Using similar chemistry, the following were prepared:

Example 182

N-{(3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pyridine-2-carboxamide
40

Mass spectrum: Found: MH^+ 584

H.p.l.c. (1) Rt 3.54min

Example 183

5 N-((3S)-1-((2S)-2-((3S)-3-((6-Chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl)isonicotinamide

Mass spectrum: Found: MH^+ 584

H.p.l.c. (1) Rt 3.18min

10 Example 184

Methyl 3-((3S)-1-((2S)-2-((3S)-3-((6-chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl)amino)-3-oxopropanoate

Mass spectrum: Found: MH^+ 579

H.p.l.c. (1) Rt 3.11min

15

Example 185

N-1-((3S)-1-((2S)-2-((3S)-3-((6-Chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl)-N-2-,N-2-dimethylglycinamide

Mass spectrum: Found: MH^+ 564

20 H.p.l.c. (1) Rt 2.63min

Example 186

Benzyl (3R)-1-((2S)-2-((3S)-3-((6-chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-ylcarbamate

25 Using Example 366 and the synthetic procedure described in Example 181, the title compound was prepared.

Mass spectrum: Found: MH^+ 613

H.p.l.c. (1) Rt 3.46min

Using similar chemistry, the following were prepared:

30

Example 187

N-((3R)-1-((2S)-2-((3S)-3-((6-Chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl)nicotinamide

Mass spectrum: Found: MH^+ 584

35 H.p.l.c. (1) Rt 3.07min

Example 188

N-((3R)-1-((2S)-2-((3S)-3-((6-Chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl)pyridine-2-carboxamide

40 Mass spectrum: Found: MH^+ 584

H.p.l.c. (1) Rt 3.38min

Example 189

5 N-{(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}isonicotinamide

Mass spectrum: Found: MH⁺ 584

H.p.l.c. (1) Rt 3.01min

Example 190

10 Methyl 3-{(3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}amino)-3-oxopropanoate

Mass spectrum: Found: MH⁺ 579

H.p.l.c. (1) Rt 3.01min

15 Example 191

N-1-{(3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}-N-2-N-2-dimethylglycinamide

Mass spectrum: Found: MH⁺ 564

H.p.l.c. (1) Rt 2.59min

20

Example 192

5'-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-2,2'-bithiophene-5-sulfonamide

25 A solution of the (3S)-3-amino-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]pyrrolidin-2-one (0.007g) in DCM (0.5ml) was treated with 5'-chloro-2,2'-bithiophene-5-sulfonyl chloride² (0.009g) and triethylamine (0.0054ml) and stirred at room temperature for 48h. The mixture was concentrated under reduced pressure and the residue purified using SPE (silica, eluting with methanol) to give the title compound (0.009g) as an off-white solid.

Mass spectrum: Found: MH⁺ 502

30 H.p.l.c. (1) Rt 3.39min

Using Intermediates 21, 22, 23 and 24, and chemistry to that described for the preparation of Example 192, the following were prepared:

Example 193

35 4'-Fluoro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1,1'-biphenyl-4-sulfonamide

Mass spectrum: Found: MH⁺ 472

H.p.l.c. (1) Rt 3.17min

40 Example 194

6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 470

H.p.l.c. (1) Rt 3.22min

5

Example 195

(E)-2-(4-Chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

Mass spectrum: Found: MH^+ 439

10 H.p.l.c. (2) Rt 5.93min

Example 196

6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide compound with 4-chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide (1:1)

15

Mass spectrum: Found: MH^+ 469

H.p.l.c. (2) Rt 6.83min

Example 197

20 6-Fluoro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 448

H.p.l.c. (1) Rt 3.03min

25 Example 198

5-Isloxazol-3-yl-N-{(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 453

H.p.l.c. (1) Rt 2.84min

30

Example 199

5-(5-Chloro-1,3,4-thiadiazol-2-yl)-N-{(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 504

35 H.p.l.c. (1) Rt 3.06min

Example 200

6-Chloro-N-{(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide compound with 4-chloro-N-{(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulphonamide

40

Mass spectrum: Found: MH^+ 470

H.p.l.c. (1) Rt 3.27min

Example 201

- 5 5'-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide

Mass spectrum: Found: MH^+ 502

H.p.l.c. (1) Rt 3.46min

- 10 Example 202

N-[(3S)-1-[(1R)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thienof[2,3-c]pyridine-2-sulfonamide

Mass spectrum: Found: MH^+ 437

H.p.l.c. (1) Rt 2.49min

15

Example 203

(E)-2-(4-Chlorophenyl)-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]ethenesulfonamide

Mass spectrum: Found: MH^+ 440

- 20 H.p.l.c. (1) Rt 3.14min

Example 204

5-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide

- 25 Mass spectrum: Found: MH^+ 470

H.p.l.c. (1) Rt 3.28min

Example 205

3-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]isoquinoline-7-sulfonamide

- 30 Mass spectrum: Found: MH^+ 465

H.p.l.c. (1) Rt 2.90min

Example 206

- 35 4-Methoxy-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]benzenesulfonamide

Mass spectrum: Found: MH^+ 409

H.p.l.c. (1) Rt 2.74min

- 40 Example 207

3-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}isoquinoline-7-sulfonamide

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 2.95min

5

Example 208

N-{(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-5-pyridin-2-ylthiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 463

10 H.p.l.c. (1) Rt 2.79min

Example 209

N-{(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-3-(1H-tetrazol-5-yl)benzenesulfonamide

15 Mass spectrum: Found: MH^+ 448

H.p.l.c. (1) Rt 2.66min

Example 210

N-{(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

20

Mass spectrum: Found: MH^+ 430

H.p.l.c. (1) Rt 2.97min

Example 211

25 N-{(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 436

H.p.l.c. (1) Rt 2.99min

30 Example 212

4-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 470

H.p.l.c. (1) Rt 3.19min

35

Example 213

N-{(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-5-(1,2,3-thiadiazol-4-yl)thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 470

40 H.p.l.c. (1) Rt 2.8min

Example 214

4-Methoxy-N-{(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}benzenesulfonamide

- 5 Mass spectrum: Found: MH^+ 410
H.p.l.c. (1) Rt 2.7min

Example 215

4'-Chloro-N-{(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1,1'-biphenyl-4-sulfonamide

- 10 Mass spectrum: Found: MH^+ 490
H.p.l.c. (1) Rt 3.42min

Example 216

15 4-Chloro-N-{(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}benzenesulfonamide

Mass spectrum: Found: MH^+ 414
H.p.l.c. (1) Rt 2.91min

20 Example 217

6-Chloro-N-{(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide compound with 4-chloro-N-{(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide

- Mass spectrum: Found: MH^+ 470
25 H.p.l.c. (1) Rt 3.28min

Example 218

(E)-2-(4-Chlorophenyl)-N-{(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

- 30 Mass spectrum: Found: MH^+ 440
H.p.l.c. (1) Rt 3.14min

Example 219

6-Chloro-N-{(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1H-benzimidazole-2-sulfonamide

- 35 Mass spectrum: Found: MH^+ 454
H.p.l.c. (1) Rt 2.55min

Example 220

5-Chloro-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 470

H.p.l.c. (1) Rt 3.29min

5

Example 221

5'-Chloro-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide

Mass spectrum: Found: MH^+ 502

10 H.p.l.c. (1) Rt 3.46min

Example 222

3-Chloro-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]isoquinoline-7-sulfonamide

15 Mass spectrum: Found: MH^+ 469

H.p.l.c. (1) Rt 3.37min

Example 223

20 5-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 470

H.p.l.c. (1) Rt 3.19min

Example 224

25 5-Chloro-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-1-benzothiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 469

H.p.l.c. (1) Rt 3.37min

30 Example 225

3-Chloro-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]isoquinoline-7-sulfonamide

Mass spectrum: Found: MH^+ 465

H.p.l.c. (1) Rt 2.87min

35

Example 226

6-Fluoro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 448

40 H.p.l.c. (1) Rt 2.4min

Example 227

5-Chloro-3-methyl-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide

5 Mass spectrum: Found: MH^+ 484

H.p.l.c. (1) Rt 3.38min

Example 228

6-Chloro-N-(3-furylmethyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

10 A solution of 6-chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide (0.015g) in THF (0.5ml) was treated with diisopropyl azodicarboxylate (0.01ml), 3-furanmethanol (0.004ml) and tri-n-butylphosphine (0.008ml) and shaken at room temperature for 60h. The mixture was concentrated under reduced
15 pressure and the residue purified by mass directed preparative h.p.l.c. to give the title compound (0.015g) as a colourless gum.

Mass spectrum: Found: MH^+ 546

H.p.l.c. (1) Rt 3.33min

Using similar chemistry, the following were prepared:

20

Example 229

6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-N-(pyridin-3-ylmethyl)naphthalene-2-sulfonamide formate

The title compound was isolated from a crude reaction mixture using mass directed
25 preparative h.p.l.c.

Mass spectrum: Found: MH^+ 557

H.p.l.c. (1) Rt 2.9min

Example 230

30 6-Chloro-N-ethyl-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 494

H.p.l.c. (1) Rt 3.32min

35 Example 231

N-{1-[(2R)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}benzamide

A solution of *tert*-butyl (2R)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-ylpropanoate (0.025g) in DCM (1ml) was treated with trifluoroacetic acid (1ml) and stirred
40 at room temperature for 2h. The mixture was then concentrated under reduced pressure to

give an oil which was subsequently treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.013g), HOBT (0.009g) and triethylamine (0.023ml). After stirring at room temperature for 1h, N-piperidin-3-ylbenzamide (0.015g) was added and stirring was continued for 48h. The reaction mixture was partitioned between DCM and
5 water. The organic extract was concentrated under reduced pressure and the residue purified using SPE (silica, eluting with cyclohexane:ethyl acetate 5:1, 3:1, 1:1, 1:3 and ethyl acetate) to give the title compound (0.012g) as a colourless gum.

Mass spectrum: Found: MH^+ 583

H.p.l.c. (1) Rt 3.32min

10

Example 232

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)naphthalene-2-sulfonamide

To a solution of (2S)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](2-oxobutyl)amino]-2-oxopyrrolidin-1-yl}propanoic acid (0.035g) in DCM (2ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.044g), HOBT (0.031g) and triethylamine (0.064ml) and the mixture was stirred at room temperature for 30min. Morpholine (0.02ml) was added and the resultant mixture stirred at room temperature for 16h. The mixture was partitioned between DCM and water. The aqueous layer was re-
15 extracted with DCM and the combined, dried (over magnesium sulphate) organic extracts were concentrated under reduced pressure. The residue was purified using mass directed preparative h.p.l.c. to give the title compound (0.008g) as a white solid.

Mass spectrum: Found: MH^+ 536

H.p.l.c. (1) Rt 3.20min

25 Using similar chemistry, the following were prepared:

Example 233

N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide

30 The title compound was prepared from Intermediate 49

Mass spectrum: Found: MH^+ 523

H.p.l.c. (1) Rt 2.87min

Example 234

35 6-Chloro-N-(2-furylmethyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

The title compound was prepared from Intermediate 63

Mass spectrum: Found: MH^+ 546

H.p.l.c. (1) Rt 3.33min

40

Example 235

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(1,3-thiazol-2-ylmethyl)naphthalene-2-sulfonamide

The title compound was prepared from Intermediate 62.

5 Mass spectrum: Found: MH^+ 563

H.p.l.c. (1) Rt 3.18min

Example 236

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(5-oxo-1,4-diazepan-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide

The title compound was prepared from Intermediate 49.

Mass spectrum: Found: MH^+ 550

H.p.l.c. (1) Rt 2.66min

15 Example 237

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide

The title compound was prepared from Intermediate 49.

Mass spectrum: Found: MH^+ 564

20 H.p.l.c. (1) Rt 2.7min

Example 238

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide

25 The title compound was prepared from Intermediate 49.

Mass spectrum: Found: MH^+ 584

H.p.l.c. (3) Rt 10.85min

Example 239

30 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpiperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide

The title compound was prepared from Intermediate 49.

Mass spectrum: Found: MH^+ 598

H.p.l.c. (3) Rt 11.3min

35

Example 240

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide

The title compound was prepared from Intermediate 49.

40 Mass spectrum: Found: MH^+ 584

H.p.l.c. (3) Rt 10.7min

Example 241

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-2-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-5-yl]-1-methyl-2-oxoethyl}-2-oxopyrrolidin-3-yl)glycinamide

The title compound was prepared from Intermediate 49.

Mass spectrum: Found: MH^+ 534

H.p.l.c. (1) Rt 2.37min

10 Example 242

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-[(1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-oxoethyl}-2-oxopyrrolidin-3-yl)glycinamide hydrobromide

The title compound was prepared from Intermediate 49.

Mass spectrum: Found: MH^+ 548

15 H.p.l.c. (3) Rt 10.3min

Example 243

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide

20 The title compound was prepared from Intermediate 49.

Mass spectrum: Found: MH^+ 550

H.p.l.c. (3) Rt 10.4min

Example 244

25 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-2-(1,4-diazepan-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide

The title compound was prepared from Intermediate 49.

Mass spectrum: Found: MH^+ 536

H.p.l.c. (3) Rt 14.5min

30

Example 245

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1-methyl-2-oxoethyl}-2-oxopyrrolidin-3-yl)glycinamide

The title compound was prepared from Intermediate 49.

35 Mass spectrum: Found: MH^+ 551

H.p.l.c. (3) Rt 13.4min

Example 246

40 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]-2-oxoethyl}-2-oxopyrrolidin-3-yl)glycinamide

The title compound was prepared from Intermediate 49.

Mass spectrum: Found: MH^+ 535

H.p.l.c. (3) Rt 12.7min

5 Example 247

6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-[(2-methyl-1,3-thiazol-4-yl)methyl]naphthalene-2-sulfonamide

The title compound was prepared from Intermediate 95.

Mass spectrum: Found: MH^+ 577

10 H.p.l.c. (1) Rt 3.24min

Example 248

6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(pyridin-2-ylmethyl)naphthalene-2-sulfonamide formate

15 The title compound was prepared from Intermediate 97.

Mass spectrum: Found: MH^+ 563

H.p.l.c. (1) Rt 3.62min

Example 249

20 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(pyridin-4-ylmethyl)naphthalene-2-sulfonamide formate

The title compound was prepared from Intermediate 96.

Mass spectrum: Found: MH^+ 557

H.p.l.c. (1) Rt 2.83min

25

Example 250

6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-[(2-methyl-1,3-thiazol-4-yl)methyl]naphthalene-2-sulfonamide formate

30 The title compound was prepared from Intermediate 95.

Mass spectrum: Found: MH^+ 644

H.p.l.c. (1) Rt 2.83min

Example 251

35 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(pyridin-4-ylmethyl)naphthalene-2-sulfonamide formate

The title compound was prepared from Intermediate 96.

Mass spectrum: Found: MH^+ 624

H.p.l.c. (1) Rt 2.74min

40

Example 252

Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}glycinate

A solution of 5'-chloro-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-2,2'-bithiophene-5-sulfonamide (0.025g) in THF (3ml) was cooled to -78°C under nitrogen, and treated with lithium bis(trimethylsilyl) amide (1.0M solution in THF; 0.092ml), followed by methyl bromoacetate (0.026ml). The resultant solution was allowed to reach room temperature and stirred for a further 22h. Methanol was added and the mixture was concentrated under reduced pressure. The residue was partitioned between DCM and water and then passed through a hydrophobic frit. The organic extract was concentrated under reduced pressure and the residue purified by mass directed preparative h.p.l.c. to give the title compound (0.006g) as a white solid.

Mass spectrum: Found: MH⁺ 574

H.p.l.c. (1) Rt 3.57min

15 Similarly prepared using the commercially available alkyl halide, was:

Example 253

5'-Chloro-N-(cyanomethyl)-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-2,2'-bithiophene-5-sulfonamide

20 Mass spectrum: Found: MH⁺ 541

H.p.l.c. (1) Rt 3.56min

Example 254

N-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}glycine

25 Using standard alkaline hydrolysis conditions, the title compound was prepared from Example 252.

Mass spectrum: Found: MH⁺ 560

H.p.l.c. (1) Rt 3.47min

30

Example 255

6-Chloro-N-{(3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

To a solution of (2R)-2-((3S)-3-[[6-chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl)propanoic acid (0.018g) in DCM (0.5ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.018g), HOBt (0.013g) and triethylamine (0.039ml) and the mixture was stirred at room temperature for 75min. 3-Methylpiperidine (0.010ml) was added and the resultant mixture stirred at room temperature for 48h. The mixture was partitioned between DCM and saturated sodium bicarbonate solution and then passed
40 through a hydrophobic frit. The organic extract concentrated under reduced pressure and

the residue was purified using SPE (silica, eluting with cyclohexane:ethyl acetate 2:1, 1:1; ethyl acetate; ethyl acetate:methanol 2:1, 1:1) to give the title compound (0.007g) as a white solid.

Mass spectrum: Found: MH^+ 478

5 H.p.l.c. (1) Rt 3.4min

Using similar chemistry, the following were prepared:

Example 256

10 N-{1-[(2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}acetamide

Mass spectrum: Found: MH^+ 521

H.p.l.c. (1) Rt 3.14min

Example 257

15 6-Chloro-N-((3S)-1-[(1R)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.36min

20 Example 258

6-Chloro-N-((3S)-1-[(1R)-1-methyl-2-[(2S)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.36min

25

Example 259

6-Chloro-N-[(3S)-1-((1R)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 549

30 H.p.l.c. (1) Rt 2.59min

Example 260

6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

35 Mass spectrum: Found: MH^+ 450

H.p.l.c. (1) Rt 3.03min

Example 261

40 6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 466

H.p.l.c. (1) Rt 2.95min

Example 262

- 5 6-Chloro-N-((3S)-1-((1R)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 521

H.p.l.c. (1) Rt 2.98min

10 Example 263

6-Chloro-N-methyl-N-((3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Using Intermediate 30 and piperidine, and the chemistry described for Example 255, the title compound was prepared.

- 15 Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.4min

Example 264

6-Chloro-N-methyl-N-((3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

- 20

Using Intermediate 55 and 3-methylpiperidine and chemistry described for Example 255, the title compound was prepared.

Mass spectrum: Found: MH^+ 494

H.p.l.c. (1) Rt 3.03min

- 25 Using similar chemistry, the following were prepared:

Example 265

N-[1-((2R)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl]acetamide

- 30 Mass spectrum: Found: MH^+ 535

H.p.l.c. (1) Rt 3.1min

Example 266

6-Chloro-N-methyl-N-((3S)-1-[(1R)-1-methyl-2-oxo-2-(3-

- 35 {[(phenylsulfonyl)amino]methyl}piperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 647

H.p.l.c. (1) Rt 3.55min

40 Example 267

6-Chloro-N-((3S)-1-((1R)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-N-methylnaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 508

H.p.l.c. (1) Rt 3.1min

5

Example 268

6-Chloro-N-((3S)-1-((1R)-2-[2-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-N-methylnaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 508

10 H.p.l.c. (1) Rt 3.23min

Example 269

6-Chloro-N-methyl-N-((3S)-1-((1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

15 Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.49min

Example 270

N-[1-((2R)-2-((3S)-3-(((6-Chloro-2-naphthyl)sulfonyl)(methyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl]benzamide

20 Mass spectrum: Found: MH^+ 597

H.p.l.c. (1) Rt 3.41min

Example 271

25 6-Chloro-N-[(3S)-1-((1R)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 563

H.p.l.c. (1) Rt 2.65min

30 Example 272

6-Chloro-N-methyl-N-((3S)-1-((1R)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.21min

35

Example 273

6-Chloro-N-methyl-N-((3S)-1-((1R)-1-methyl-2-[(2S)-2-methylpiperidin-1-yl]-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 492

40 H.p.l.c. (1) Rt 3.49min

Example 274

N-[(3S)-1-[(1R)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloro-N-methylnaphthalene-2-sulfonamide

5 Mass spectrum: Found: MH^+ 492

H.p.l.c. (1) Rt 3.41min

Example 275

6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-(4-pyrrolidin-1-ylpiperidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

10

Mass spectrum: Found: MH^+ 547

H.p.l.c. (1) Rt 2.68min

Example 276

15 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 561

H.p.l.c. (1) Rt 2.77min

20 Example 277

6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-(4-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 492

H.p.l.c. (1) Rt 3.58min

25

Example 278

N-[(3S)-1-[(1R)-2-(4-[(Benzylsulfonyl)amino]methyl)piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloro-N-methylnaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 661

30 H.p.l.c. (1) Rt 3.52min

Example 279

N-[1-((2R)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl)piperidin-4-yl]benzamide

35 Mass spectrum: Found: MH^+ 597

H.p.l.c. (1) Rt 3.38min

Example 280

N-[1-((2R)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl)pyrrolidin-3-yl]benzamide

40

Mass spectrum: Found: MH^+ 583

H.p.l.c. (1) Rt 3.32min

Example 281

- 5 N-[1-((2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl)piperidin-2-yl]methyl}benzamide

Mass spectrum: Found: MH^+ 611

H.p.l.c. (1) Rt 3.52min

10 Example 282

N-[1-((2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl)piperidin-4-yl]acetamide

Mass spectrum: Found: MH^+ 535

H.p.l.c. (1) Rt 3.04min

15

Example 283

N-[1-((2R)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl)pyrrolidin-3-yl]acetamide

Mass spectrum: Found: MH^+ 521

- 20 H.p.l.c. (1) Rt 2.99min

Example 284

6-Chloro-N-methyl-N-((3S)-1-((1R)-1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

- 25 Mass spectrum: Found: MH^+ 575

H.p.l.c. (1) Rt 3.42min

Example 285

6-Chloro-N-((3S)-1-((1R)-2-[4-(dimethylamino)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-N-methylnaphthalene-2-sulfonamide

- 30 Mass spectrum: Found: MH^+ 521

H.p.l.c. (1) Rt 2.65min

Example 286

- 35 6-Chloro-N-((3S)-1-((1R)-2-[4-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-N-methylnaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 508

H.p.l.c. (1) Rt 3.11min

40 Example 287

6-Chloro-N-[(3S)-1-[(1R)-2-(4-methoxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 508

H.p.l.c. (1) Rt 3.29min

5

Example 288

6-Chloro-N-[(3S)-1-[(1R)-2-(3-methoxypiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 508

10 H.p.l.c. (1) Rt 3.35min

Example 289

6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

15 Mass spectrum: Found: MH^+ 479

H.p.l.c. (1) Rt 3.18min

Example 290

20 6-Chloro-N-methyl-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

The title compound was prepared from Intermediate 30.

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.25min

25 Example 291

6-Chloro-N-methyl-N-[(3R)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

The title compound was prepared from Intermediate 30.

Mass spectrum: Found: MH^+ 492

30 H.p.l.c. (1) Rt 3.51min

Example 292

6-Chloro-N-[(3R)-1-[(1S)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide

35 The title compound was prepared from Intermediate 30.

Mass spectrum: Found: MH^+ 563

H.p.l.c. (1) Rt 2.82min

Example 293

6-Chloro-N-(cyanomethyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

A solution of 6-chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide (0.01g) in THF (2ml) was cooled to -78°C under nitrogen, and treated with lithium bis(trimethylsilyl) amide (1.0M solution in THF; 0.026ml), followed by bromoacetonitrile (0.013g). The resultant solution was allowed to reach room temperature and stirred for a further 16h. The mixture was then cooled to -78°C and further lithium bis(trimethylsilyl) amide (0.026ml) added. After reaching room temperature, the reaction mixture was stirred for a further 18h and then quenched by the addition of methanol (1ml). The resultant solution was concentrated under reduced pressure and the residue purified by mass directed preparative h.p.l.c. to give the title compound (0.003g) as a white solid.

Mass spectrum: Found: MH^+ 505

H.p.l.c. (1) Rt 3.16min

Similarly prepared using commercially available alkyl halides, were:

Example 294

6-Chloro-N-methyl-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 480

H.p.l.c. (1) Rt 3.11min

Example 295

6-Chloro-N-(3,3-dimethyl-2-oxobutyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 564

H.p.l.c. (1) Rt 3.39min

Example 296

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N1-methyl-N2-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide

Mass spectrum: Found: MH^+ 537

H.p.l.c. (1) Rt 2.98min

Example 297

N-Allyl-6-chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 506

H.p.l.c. (1) Rt 3.26min

Example 298

Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinate

Mass spectrum: Found: MH^+ 538

H.p.l.c. (1) Rt 3.12min

5

Example 299

Ethyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinate

Mass spectrum: Found: MH^+ 552

10 H.p.l.c. (1) Rt 3.36min

Example 300

tert-Butyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinate

15 Mass spectrum: Found: MH^+ 580

H.p.l.c. (1) Rt 3.45min

Example 301

20 N-[1-((2R)-2-[(3R)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl]benzamide

Using Example 327 and the synthetic procedure described for Intermediate 52, the title compound was prepared.

Mass spectrum: Found: MH^+ 597

H.p.l.c. (1) Rt 3.37min

25

Example 302

N-[(3R)-1-[(1R)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloro-N-methylnaphthalene-2-sulfonamide

30 Using Example 328 and the synthetic procedure described for Intermediate 52, the title compound was prepared.

Mass spectrum: Found: MH^+ 491

H.p.l.c. (1) Rt 3.4min

Example 303

35 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycine

40 To a solution of methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinate (0.010g) in THF (2ml) was added lithium hydroxide (0.003g) in water (2ml), and the resultant solution stirred for 16h. The mixture was acidified to pH5 using hydrochloric acid (2N), and then concentrated under

reduced pressure. The residue was purified using mass directed preparative h.p.l.c. to give the title compound (0.006g) as a white solid.

Mass spectrum: Found: MH^+ 524

H.p.l.c. (1) Rt 3.00min

5

Example 304

1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidine-2-carboxylic acid

To a solution of (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid (0.025g) in DCM (10ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.036g), HOBT (0.026g) and triethylamine (0.026ml) and the mixture was stirred at room temperature for 30min. Ethyl pipercolinate (0.030g) was added and the resultant mixture stirred at room temperature for 16h. The mixture was partitioned between DCM and water. The aqueous layer was re-extracted with DCM and the combined, dried (over magnesium sulphate) organic extracts were concentrated under reduced pressure. The residue was then dissolved in a mixture of THF (1ml) and water (1ml), treated with lithium hydroxide (0.005g) and stirred at room temperature for 18h. The reaction mixture was acidified to pH5 using hydrochloric acid (2N) and concentrated under reduced pressure. The residue was purified using SPE (aminopropyl stationary phase, washed with methanol and eluted with 10% hydrochloric acid in methanol) to give the title compound (0.007g) as white solid.

Mass spectrum: Found: MH^+ 508

H.p.l.c. (1) Rt 3.09min

25 Example 305

6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

A solution of *tert*-butyl (2R)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoate (0.025g) in DCM (3ml) was treated with trifluoroacetic acid (3ml) and stirred at room temperature for 2h. The mixture was then concentrated under reduced pressure to give an oil which was subsequently treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.013g), HOBT (0.009g) and triethylamine (0.023ml). After stirring at room temperature for 1h, piperidine (0.007ml) was added and stirring was continued for 48h. The reaction mixture was partitioned between DCM and water. The organic extract was concentrated under reduced pressure and the residue purified using SPE (silica, eluting with cyclohexane:ethyl acetate 5:1, 3:1, 1:1, 1:3 and ethyl acetate) to give the title compound (0.021g) as a colourless gum.

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.27min

40

Example 3066-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

To a solution of (2S)-2-[(3S)-3-[[[6-chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl]propanoic acid (0.020g) in DCM (2ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.011g), HOBT (0.007g) and triethylamine (0.020ml) and the mixture was stirred at room temperature for 30min. Piperidine (0.006ml) was added and the resultant mixture stirred at room temperature for 16h. The mixture was partitioned between DCM and water. The aqueous layer was re-
 10 extracted with DCM and the combined, dried (over magnesium sulphate) organic extracts were concentrated under reduced pressure. The residue was purified using mass directed preparative h.p.l.c. to give the title compound (0.002g) as a colourless gum.

Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.51min

15 Using similar chemistry, the following were prepared:

Example 3076-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

20 Mass spectrum: Found: MH^+ 492

H.p.l.c. (1) Rt 3.61min

Example 3086-Chloro-N-[(3S)-1-[(1S)-2-[2-[(diethylamino)methyl]piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide

25 Mass spectrum: Found: MH^+ 563

H.p.l.c. (1) Rt 2.88min

Example 3096-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.48min

35 Example 310Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinate

To a solution of (2S)-2-[(3S)-3-[[[6-chloro-2-naphthyl)sulfonyl](2-methoxy-2-oxoethyl)amino]-2-oxopyrrolidin-1-yl]propanoic acid (0.032g) in DCM (5ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.02g), HOBT (0.014g) and
 40

triethylamine (0.034ml) and the mixture was stirred at room temperature for 1h. Piperidine (0.01ml) was added and the resultant mixture stirred at room temperature for 72h. The mixture was concentrated under reduced pressure and the residue purified using mass directed preparative h.p.l.c. to give the title compound (0.017g) as a white solid.

5 Mass spectrum: Found: MH^+ 536
H.p.l.c. (1) Rt 3.54min

Example 311

N-[(6-Chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycine

10 To a solution of methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinate (0.010g) in THF (1ml) was added lithium hydroxide (0.005g) in water (1ml), and the resultant solution stirred for 16h. The mixture was acidified to pH5 using hydrochloric acid (2N), and then concentrated under reduced
15 pressure. The residue was purified using SPE (eluting with methanol and then 10% HCl/methanol) to give the title compound (0.01g) as a white solid.

Mass spectrum: Found: MH^+ 522
H.p.l.c. (1) Rt 3.29min

20 Example 312

6-Chloro-N-(cyanomethyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

A solution of 6-chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide (0.015g) in THF (2ml) was cooled to -78°C under nitrogen,
25 and treated with lithium bis(trimethylsilyl) amide (1.0M solution in THF; 0.042ml), followed by bromoacetonitrile (0.019g). The resultant solution was allowed to reach room temperature and stirred for a further 16h. The mixture was then cooled to -78°C and further lithium bis(trimethylsilyl) amide (0.042ml) added. After reaching room temperature, the reaction mixture was stirred for a further 18h and then quenched by the addition of methanol (1ml).
30 The resultant solution was concentrated under reduced pressure and the residue partitioned between water and DCM. The organic layer was separated, dried (over magnesium sulphate) and concentrated under reduced pressure. The residue was purified by mass directed preparative h.p.l.c to give the title compound (0.007g) as a colourless gum.

Mass spectrum: Found: MH^+ 503
35 H.p.l.c. (1) Rt 3.35min

Similarly prepared using commercially available alkyl halides, were:

Example 313

N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinamide

40

160

Mass spectrum: Found: MH^+ 521

H.p.l.c. (1) Rt 3.07min

Example 314

5 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl)-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 534

H.p.l.c. (1) Rt 3.39min

10 Example 315 and Example 316

N-Allyl-6-chloro-N-((1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide [Isomer 1 and Isomer 2]

The title compounds were prepared by alkylation of Example 2 with allyl iodide, followed by purification using mass directed preparative h.p.l.c..

15 Isomer 1

Mass spectrum: Found: MH^+ 504

H.p.l.c. (1) Rt 3.5min

Isomer 1

Mass spectrum: Found: MH^+ 504

20 H.p.l.c. (1) Rt 3.52min

Example 317

N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-((3S)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)glycinamide

- 25 A solution of 6-chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide (0.01g) in THF (2ml) was cooled to -78°C under nitrogen, and treated with lithium bis(trimethylsilyl) amide (1.0M solution in THF; 0.023ml), followed by 2-bromoacetamide (0.012g). The resultant solution was allowed to reach room temperature and stirred for a further 16h. The mixture
- 30 was then cooled to -78°C and further lithium bis(trimethylsilyl) amide (0.023ml) added. After reaching room temperature, the reaction mixture was stirred for a further 16h and then quenched by the addition of methanol (1ml). The resultant solution was concentrated under reduced pressure and the residue partitioned between water and DCM. The organic layer was separated, dried (over magnesium sulphate) and concentrated under reduced pressure.
- 35 The residue was purified by mass directed preparative h.p.l.c. to give the title compound (0.001g) as a white solid.

Mass spectrum: Found: MH^+ 590

H.p.l.c. (1) Rt 2.77min

Similarly prepared using commercially available alkyl halides, were:

Example 318

Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-((3S)-1-{(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycinate formate

Mass spectrum: Found: MH^+ 605

5 H.p.l.c. (1) Rt 2.62min

Example 319

6-Chloro-N-((3S)-1-{(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide

10 Mass spectrum: Found: MH^+ 603

H.p.l.c. (1) Rt 2.81min

Example 320 and Example 321

N-[(6-Chloro-2-naphthyl)sulfonyl]-N-(1-{1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine formate [Isomer 1 and Isomer 2]

15 The title compounds were prepared by alkaline hydrolysis (LiOH) of Example 318, followed by purification using mass directed preparative h.p.l.c..

Isomer 1

Mass spectrum: Found: MH^+ 591

20 H.p.l.c. (1) Rt 2.6min

Isomer 1

Mass spectrum: Found: MH^+ 591

H.p.l.c. (1) Rt 2.63min

25 Example 322

N-[(6-Chloro-2-naphthyl)sulfonyl]-N-((3S)-1-{(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine

The title compound was prepared by trifluoroacetic acid hydrolysis of Intermediate 88, followed by purification using mass directed preparative h.p.l.c..

30 Mass spectrum: Found: MH^+ 591

H.p.l.c. (1) Rt 2.85min

Example 323

N-[1-((2R)-2-{(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-yl]benzamide

35 A solution of *tert*-butyl (2R)-2-{(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl}propanoate (0.017g) in DCM (0.5ml) was treated with trifluoroacetic acid (0.5ml) and stirred at room temperature for 2h. The mixture was then concentrated under reduced pressure to give an oil which was subsequently treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.01g), HOBt (0.007g) and

40

triethylamine (0.020ml). After stirring at room temperature for 1h, N-piperidin-3-ylbenzamide (0.010g) was added and stirring was continued for 16h. The reaction mixture was partitioned between DCM and water. The organic extract was concentrated under reduced pressure and the residue purified using SPE (silica, eluting with cyclohexane:ethyl acetate 3:1, 1:1, 5 1:3, ethyl acetate) to give the title compound (0.012g) as a pale yellow gum.

Mass spectrum: Found: MH^+ 597

H.p.l.c. (1) Rt 3.35min

Note: Example 323 = Example 270.

Using the procedure described above, the following compounds were also prepared:

10

Example 324

6-Chloro-N-methyl-N-((3S)-1-{(1R)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl}-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 492

15 H.p.l.c. (1) Rt 3.57min

Example 325

N-((3S)-1-{(1R)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl}-2-oxopyrrolidin-3-yl)-6-chloro-N-methylnaphthalene-2-sulfonamide

20 Mass spectrum: Found: MH^+ 490

H.p.l.c. (1) Rt 3.18min

Example 326

6-Chloro-N-{(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

25

Using Intermediate 32 and the procedure described for Example 1, the title compound was prepared.

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.35min

30 Using similar chemistry, the following were prepared:

Example 327

N-{1-[(2R)-2-((3R)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}benzamide (two diastereoisomers)

35 Mass spectrum: Found: MH^+ 583

H.p.l.c. (1) Rt 3.26 & 3.44min

Example 328

N-{(3R)-1-[(1R)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-6-chloronaphthalene-2-sulfonamide

40

Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.29min

Example 329

5 6-Chloro-N-((3R)-1-[(1R)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 466

H.p.l.c. (1) Rt 2.95min

10 Example 330

6-Chloro-N-((3R)-1-[(1R)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 450

H.p.l.c. (1) Rt 3.05min

15

Example 331

6-Chloro-N-((3R)-1-[(1R)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 478

20 H.p.l.c. (1) Rt 3.29min

Example 332

6-Chloro-N-((3R)-1-[(1R)-1-methyl-2-[(2S)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

25 Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.29min

Example 333

30 6-Chloro-N-[(3R)-1-[(1R)-2-{2-[(diethylamino)methyl]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 549

H.p.l.c. (1) Rt 2.66min

Example 334

35 N-((3R)-1-[(1R)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 476

H.p.l.c. (1) Rt 3.15min

40 Example 335

6-Chloro-N-{1-[(1R)-1-methyl-2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

Using Intermediate 37, and the synthetic procedure described for Example 1, the title compound was prepared.

5 Mass spectrum: Found: MH^+ 479

H.p.l.c. (1) Rt 2.92min

Using similar chemistry, the following were prepared:

Example 336

10 6-Bromo-N-{1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide

The title compound was prepared using Intermediate 119.

Mass spectrum: Found: MH^+ 509

H.p.l.c. (1) Rt 3.26min

15

Example 337

5-Chloro-3-methyl-N-{1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide

The title compound was prepared using Intermediate 120.

20 Mass spectrum: Found: MH^+ 484

H.p.l.c. (1) Rt 3.31min

Example 338

25 3-Chloro-N-{1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}isoquinoline-7-sulfonamide

Using Intermediate 40, and the synthetic procedure described for Example 1, the title compound was prepared.

Mass spectrum: Found: MH^+ 465

H.p.l.c. (1) Rt 2.84min

30

Example 339

3'-Chloro-N-{1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-1,1'-biphenyl-4-sulfonamide

35 Using Intermediate 39, and the synthetic procedure described for Example 1, the title compound was prepared.

Mass spectrum: Found: MH^+ 490

H.p.l.c. (1) Rt 3.34min

Example 340

7-Hydroxy-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

n-Butylamine (1ml) was added to a suspension of Intermediate 51 (0.015g) in dry THF (1ml), stirred at room temperature for 5h and concentrated under reduced pressure. The residue was partitioned between DCM and water. The separated organic extract was passed through a hydrophobic frit and the filtrate concentrated under reduced pressure to give the title compound (0.0035g) as an oil.

Mass spectrum: Found: MH^+ 446

H.p.l.c. (1) Rt 3.05min

10

Example 341

6-Chloro-N-methyl-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Using Intermediate 56 and the procedure described for Example 1, the title compound was prepared.

Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.49min

Using similar chemistry, the following were prepared:

20 Example 342

6-Chloro-N-methyl-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-pyrrolidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.25min

25

Example 343

6-Chloro-N-[(3R)-1-[(1R)-2-[2-[(diethylamino)methyl]piperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-methylnaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 563

30 H.p.l.c. (1) Rt 2.74min

Example 344

N-[(3R)-1-[(1R)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-6-chloro-N-methylnaphthalene-2-sulfonamide

35 Mass spectrum: Found: MH^+ 490

H.p.l.c. (1) Rt 3.29min

Example 345

6-Chloro-N-methyl-N-[(3R)-1-[(1R)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

40

Mass spectrum: Found: MH^+ 492

H.p.l.c. (1) Rt 3.43min

Example 346

5 6-Chloro-N-((3S)-1-((1S)-2-[3-(ethylamino)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

To a solution of acetaldehyde (0.041ml from a stock solution made up from 0.0127l acetaldehyde dissolved in 1ml DCM) in dry DCM (0.4ml) treated with acetic acid (0.1ml from a stock solution made up from 0.0054ml acetic acid dissolved in 1ml DCM) was added

- 10 N-((3S)-1-((1S)-2-(3-aminopiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide [Example 365] (0.045g) followed by tetraethylammonium triacetoxyborohydride (0.005g). The mixture was stirred at room temperature, under nitrogen, for 60h. DCM (1ml) was added and the resultant solution washed with saturated sodium bicarbonate (1ml) in a hydrophobic frit. The solvent was concentrated under reduced
- 15 pressure and the residue purified by mass directed preparative h.p.l.c. to give the title compound (0.8mg) as an oil.

Mass spectrum: Found: MH^+ 507

H.p.l.c. (2) Rt 6.22min

Similarly prepared using commercially available aldehydes, were:

20

Example 347

6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1H-pyrrol-2-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 558

25 H.p.l.c. (2) Rt 5.21min

Example 348

6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

30 Mass spectrum: Found: MH^+ 570

H.p.l.c. (2) Rt 5.18min

Example 349

6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-hydroxybutyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

35

Mass spectrum: Found: MH^+ 551

H.p.l.c. (2) Rt 6.9min

Example 350

6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-4-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 570

H.p.l.c. (2) Rt 5.76min

5

Example 351

N-{(3S)-1-[(1S)-2-(3-[(2-Aminopyrimidin-5-yl)methyl]amino)piperidin-1-yl]-1-methyl-2-oxoethyl}-2-oxopyrrolidin-3-yl}-6-chloronaphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 586

10 H.p.l.c. (2) Rt 6.42min

Example 352

6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-2-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

15 Mass spectrum: Found: MH^+ 570

H.p.l.c. (2) Rt 5.89min

Example 353

6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1H-pyrazol-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

20

Mass spectrum: Found: MH^+ 559

H.p.l.c. (2) Rt 7.3min

Example 354

25 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-4-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 570

H.p.l.c. (2) Rt 5.69min

30 Example 355

6-Chloro-N-((3S)-1-{(1S)-2-[3-({5-(hydroxymethyl)-2-furyl}methyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 589

H.p.l.c. (2) Rt 7.1min

35

Example 356

6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1,3-thiazol-2-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 576

40 H.p.l.c. (2) Rt 5.89min

Example 357

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-(3-[(1-methyl-1H-imidazol-2-yl)methyl]amino)piperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

5 Mass spectrum: Found: MH^+ 573

H.p.l.c. (2) Rt 4.22min

Example 358

10 6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-hydroxy-2,2-dimethylpropyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 565

H.p.l.c. (2) Rt 7.4min

Example 359

15 6-Chloro-N-[(3S)-1-((1S)-2-{3-[(1H-imidazol-4-ylmethyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 559

H.p.l.c. (2) Rt 9.42min

20 Example 360

6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-ethoxy-2-oxopropyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 581

H.p.l.c. (2) Rt 6.21min

25

Example 361

6-Chloro-N-[(3S)-1-((1S)-2-{3-[(3-methoxypropyl)amino]piperidin-1-yl}-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 551

30 H.p.l.c. (2) Rt 7.75min

Example 362

4-[(1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl)amino)methyl]-1-methylpyridinium iodide

35 Mass spectrum: Found: MH^+ 588

H.p.l.c. (2) Rt 4.75min

Example 363

40 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-(3-[(5-methyl-1H-imidazol-4-yl)methyl]amino)piperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 573

H.p.l.c. (2) Rt 5.03min

Example 364

5 Benzyl (3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate

A solution of (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid (0.408g) in DCM (21ml) was treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.394g), HOBt (0.278g) and triethylamine (0.286ml) and
10 stirred at room temperature for 1h. A solution of benzyl (3S)-piperidin-3-ylcarbamate (0.361g) in DCM (1ml) was then added and stirring continued for 72h. The mixture was partitioned between DCM and water. The separated organic extracts were washed with water and brine, dried (over magnesium sulphate), and concentrated under reduced pressure. The residue was purified using BiotageTM chromatography (eluting with
15 hexane:ethyl acetate 1:7→1:10) to give the title compound (0.268g) as an oil.

Mass spectrum: Found: MH^+ 613

H.p.l.c. (1) Rt 3.59min

Example 365

20 N-((3S)-1-[(1S)-2-[(3S)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide

Benzyl (3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate (0.128g) was dissolved in DCM (3.5ml) and treated with trifluoroacetic acid (10.5ml) and stirred at room temperature for 6h. The mixture was
25 concentrated under reduced pressure and the residue purified by SPE (acid ion-exchange, eluting with ethyl acetate:methanol 9:1) to give the title compound (0.093g) as a colourless oil.

Mass spectrum: Found: MH^+ 480

H.p.l.c. (1) Rt 2.75min

30

Example 366

N-((3S)-1-[(1S)-2-[(3R)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide

Using benzyl (3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate and the synthetic procedure described for Example
35 365, the title compound was prepared.

Mass spectrum: Found: MH^+ 480

H.p.l.c. (1) Rt 2.55min

40 Example 367

5-(4-Chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-(1-piperidinyl)ethyl]-2-oxopyrrolidinyl}-2-thiophenesulfonamide

A mixture of 5-bromo-N-[2-methoxy-4-(2-polystyrylethoxy)benzyl]-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-(1-piperidinyl)ethyl]-2-oxopyrrolidinyl}-2-thiophenesulfonamide (0.025g), sodium carbonate (0.0017g), 4-chlorobenzeneboronic acid (0.0042g), tetrakis(triphenylphosphine) palladium(0) (0.0015g) and tetrahydrofuran-water (4:1, 0.5ml) was stirred gently at in a sealed vessel at 78°C for 72h. The resin was filtered, washed with DMF, 0.2N HCl, methanol and then DCM. The dried resin was then treated with trifluoroacetic acid-DCM (1:1, 0.5ml), shaken at room temperature for 1h and filtered. The resultant filtrate was concentrated under reduced pressure to give the title compound (0.0026g) as an off-white glass.

Mass spectrum: Found: MH^+ 496

H.p.l.c. (1) Rt 3.39min

Using similar chemistry, the following were prepared:

15

Example 368

N-{(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-5-phenylthiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 462

20 H.p.l.c. (1) Rt 3.2min

Example 369

5-(4-Hydroxyphenyl)-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}thiophene-2-sulfonamide

25 Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 2.98min

Example 370

5-(3-Methoxyphenyl)-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}thiophene-2-sulfonamide

30 Mass spectrum: Found: MH^+ 492

H.p.l.c. (1) Rt 3.23min

Example 371

35 N-{(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}-5-(4-methylphenyl)thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 476

H.p.l.c. (1) Rt 3.35min

40 Example 372

5-(3-Chlorophenyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 487

H.p.l.c. (1) Rt 3.46min

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Example 373

5-(2-Chlorophenyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 496

10 H.p.l.c. (1) Rt 3.31min

Example 374

5-(2,3-Dichlorophenyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide

15 Mass spectrum: Found: MH^+ 530

H.p.l.c. (1) Rt 3.47min

Example 375

5-(2-Fluoro-4-methylphenyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-

20 oxopyrrolidin-3-yl]thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 492

H.p.l.c. (1) Rt 3.35min

Example 376

25 5-(6-Amino-5-methylpyridin-3-yl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 492

H.p.l.c. (1) Rt 2.13min

30 Example 377

N-[(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.26min

35

Example 378

5-(3-Furyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 451

40 H.p.l.c. (1) Rt 3.35min

Example 379

N-[(3S)-1-[(1S)-1-Methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,3'-bithiophene-5-sulfonamide

- 5 Mass spectrum: Found: MH^+ 468
H.p.l.c. (1) Rt 3.47min

Example 380

5-(3-Aminophenyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide

- 10 Mass spectrum: Found: MH^+ 477
H.p.l.c. (1) Rt 3.01min

Example 381

- 15 5-(2-Fluorophenyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 480
H.p.l.c. (1) Rt 3.56min

20 Example 382

5-(2-Hydroxyphenyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 478
H.p.l.c. (1) Rt 3.41min

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Example 383 and Example 384

N-[(6-Chloro-2-naphthyl)sulfonyl]-N-(1-{1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine formate [Isomer 1 and Isomer 2]

- 30 To a solution of benzyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)glycinate compound with formic acid (1:1) (0.060g) in methanol (4ml) were added potassium carbonate (0.3g) and water (2ml) and the mixture left to stir for 5h. The mixture was concentrated under reduced pressure and the inorganics removed using SPE (6g OASISTM HLB Extraction Cartridge, eluting with water and then methanol) to give a clear gum, which was purified by
35 mass directed preparative h.p.l.c. to give the title compounds (Isomer 1, 0.011g; Isomer 2, 0.016g) as white solids.

Isomer 1

Mass spectrum: Found: MH^+ 591
H.p.l.c. (1) Rt 2.42min

- 40 Isomer 2

Mass spectrum: Found: MH^+ 591

H.p.l.c. (1) Rt 2.46min

Example 385

5 5-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-1-benzofuran-2-sulfonamide

To a solution of (3S)-3-amino-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one (0.077g) in anhydrous acetonitrile (2ml) were added 5-chloro-1-benzofuran-2-sulfonyl chloride (0.043g) in acetonitrile (2ml) and pyridine (0.057ml), and the mixture was stirred at
10 room temperature for 72h. Saturated ammonium chloride solution (2ml) was added and the resultant mixture stirred at room temperature for 20min. The mixture was concentrated under reduced pressure and the residue partitioned between chloroform and hydrochloric acid (2M). The organic layer was washed with saturated sodium bicarbonate and brine. The organic layer was isolated, dried (over magnesium sulphate) and concentrated under
15 reduced pressure to give the title compound (0.043g) as a white solid.

Mass spectrum: Found: MH^+ 456

H.p.l.c. (1) Rt 2.78min

Example 386

20 (E)-2-(5-Chlorothiophen-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide

Route 1

To a solution of (3S)-3-amino-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one (14.9g) in anhydrous acetonitrile (750ml) were added (E)-2-(5-chlorothiophen-2-yl)ethanesulfonyl chloride (16.5g) in acetonitrile (250ml) and pyridine (11ml), and the mixture
25 was stirred at room temperature for 72h. Saturated ammonium chloride solution was added and the resultant mixture stirred at room temperature for 30min. The mixture was concentrated under reduced pressure and the residue partitioned between chloroform and a 1:1 mixture of hydrochloric acid (2M) and water. The organic layer was washed with a 1:1
30 mixture of saturated sodium bicarbonate and water, and brine. The organic layer was isolated, dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (19.3g) as a white solid.

Mass spectrum: Found: MH^+ 448

H.p.l.c. (1) Rt 2.99min

35 1H NMR ($CDCl_3$): δ 7.48(1H, d), 7.08(1H, d), 6.90(1H, d), 6.55(1H, d), 5.12(1H, br.d), 5.06(1H, q), 3.96(1H, m), 3.70-3.48(9H, m), 3.35(1H, m), 2.62(1H, m), 2.05(1H, m), 1.34(3H, d) ppm.

Route 2

To a mixture of N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide (0.028g), tris(dibenzylideneacetone)dipalladium (0) (0.0028g) and 2-
40

(di-*t*-butylphosphino)biphenyl (0.0037g) under nitrogen, was added dry dioxan (0.25ml) and the mixture was stirred for 5min at room temperature. N,N-Di-isopropylethylamine (0.02ml) followed by 2-bromo-5-chlorothiophene (0.016ml) in dry dioxan (0.25ml) were then added and the resultant solution was stirred at room temperature for 19h and then heated at 80°C for 1h. The reaction was lowered to 60°C and maintained at this temperature for 20h. Evaporation of the cooled reaction mixture under a stream of nitrogen gave a residue that was purified by SPE (silica; using an OPTIX. Gradient elution [flow rate 10ml/min; fraction size 10ml; UV detector set at λ_{max} 254nm; 0 to 50% ethyl acetate -cyclohexane over 5min, followed by 50% to 100% ethyl acetate-cyclohexane for 11min and then 100% ethyl acetate for 4min]) gave the title compound (0.0187g) as a clear oil.

Using similar chemistry to that described for Example 386 Route 1, the following were prepared:

Example 387

15 5-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide

Mass spectrum: Found: MH⁺ 472

H.p.l.c. (1) Rt 2.9min

¹H NMR (CDCl₃): δ 7.87(1H, d), 7.86(1H, m), 7.78(1H, dm), 7.46(1H, dd), 5.58(1H, br.d), 5.02(1H, q), 3.91(1H, m), 3.69-3.44(9H, m), 3.34(1H, m), 2.65(1H, m), 2.10(1H, m), 1.31(3H, d) ppm.

Example 388

25 6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide

Mass spectrum: Found: MH⁺ 472

H.p.l.c. (1) Rt 2.96min

¹H NMR (CDCl₃): δ 7.89(1H, s), 7.85(1H, br.m), 7.81(1H, d), 7.44(1H, dd), 5.46(1H, br.d), 5.01(1H, q), 3.90(1H, m), 3.73-3.48(9H, m), 3.34(1H, m), 2.67(1H, m), 2.10(1H, m), 1.31(3H, d) ppm.

Example 389

35 5-Chloro-3-methyl-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide

Mass spectrum: Found: MH⁺ 486

H.p.l.c. (1) Rt 3.11min

Example 390

40 3-Cyano-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}benzenesulfonamide

175

Mass spectrum: Found: MH^+ 407

H.p.l.c. (1) Rt 2.4min

Example 391

5 4-Cyano-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]benzenesulfonamide

Mass spectrum: Found: MH^+ 407

H.p.l.c. (1) Rt 2.4min

10 Example 392

5-(5-Chloro-1,3,4-thiadiazol-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]thiophene-2-sulfonamide

Mass spectrum: Found: MH^+ 506

H.p.l.c. (1) Rt 2.82min

15 Two additional compounds, Examples 440 and 441 were prepared using similar chemistry.

Example 393

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide

20 Using Example 388 and 1-bromo-2-butanone, and the synthetic procedure described for Example 293, the title compound was prepared.

Mass spectrum: Found: MH^+ 542

H.p.l.c. (1) Rt 3.28min

Using similar chemistry, the following was prepared:

25

Example 394

N2-[(6-Chloro-1-benzothien-2-yl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide

Mass spectrum: Found: MH^+ 529

30 H.p.l.c. (1) Rt 2.86min

Example 395

5-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide

35 Using Example 387 and 1-bromo-2-butanone, and the synthetic procedure described for Example 293, the title compound was prepared.

Mass spectrum: Found: MH^+ 542

H.p.l.c. (1) Rt 3.27min

Using similar chemistry, the following was prepared:

40

Example 396

N2-[(5-Chloro-1-benzothien-2-yl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide

Mass spectrum: Found: MH^+ 529

5 H.p.l.c. (1) Rt 2.85min

Example 397

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-phenylnaphthalene-2-sulfonamide

- 10 A mixture of Example 1 (0.0206g), phenylboronic acid (0.0162mg), copper (II) acetate (0.016g), triethylamine 0.123ml) and powered 4Å molecular sieves (dried, 0.1g) in dry DCM (0.5ml) was stirred at room temperature for 6 days. The reaction mixture was filtered using SPE (silica, eluting with 30% methanol in ethyl acetate). The organic fraction was concentrated under reduced pressure to give a brown residue that was purified by mass
- 15 directed preparative h.p.l.c. to give the title compound (0.0062g) as a gum.

Mass spectrum: Found: MH^+ 542

H.p.l.c. (1) Rt 3.38min

Using similar chemistry, the following were prepared:

20 Example 398

6-Chloro-N-(4-fluorophenyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 560

H.p.l.c. (1) Rt 3.43min

25

Example 399

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-pyridin-4-yl-naphthalene-2-sulfonamide

Mass spectrum: Found: MH^+ 543

30 H.p.l.c. (1) Rt 3.06min

Example 400

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-pyridin-3-yl-naphthalene-2-sulfonamide

35 Mass spectrum: Found: MH^+ 543

H.p.l.c. (1) Rt 3.10min

Example 401

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-thien-3-yl-naphthalene-2-sulfonamide

40

Mass spectrum: Found: MH^+ 548

H.p.l.c. (1) Rt 3.38min

Example 402

5 5-Bromo-N-((3S)-1-((1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl)-2-oxopyrrolidin-3-yl)thiophene-2-sulfonamide

Intermediate 99 (0.025g of resin) was treated with trifluoroacetic acid-DCM (1:1, 1ml) and shaken for 2h and filtered. The filtrate was concentrated under a stream of nitrogen to give the title compound (0.0025g) as an off-white glass.

10 Mass spectrum: Found: MH^+ 465

H.p.l.c. (1) Rt 3.09min

Example 403

15 N-((3S)-1-((1S)-2-((3R)-3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate and

Example 404

Benzyl (3R)-1-((2S)-2-((3S)-3-((2-naphthylsulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-ylcarbamate

A mixture of benzyl (3R)-1-((2S)-2-((3S)-3-((6-chloro-2-naphthyl)sulfonyl)amino)-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-ylcarbamate (0.350g), 10% palladium on carbon (0.035g) and ethanol (1000ml) was stirred under an atmosphere of hydrogen for 17h. The reaction mixture was filtered through Harbolite™ and the filtrate was concentrated under reduced pressure to give an oil. The oil was partially purified using SPE (silica, eluting with methanol and then 10% aqueous ammonia in methanol) and then fully purified using mass
25 directed preparative h.p.l.c. to give the title compounds (Example 403, 0.01g; Example 404, 0.028g), both as oils.

Example 403

Mass spectrum: Found: MH^+ 445

30 H.p.l.c. (1) Rt 2.37min

Example 404

Mass spectrum: Found: MH^+ 577

H.p.l.c. (1) Rt 3.27min

35

Example 405

N-((3S)-1-((1S)-2-((3S)-3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate and

Example 406

Benzyl (3S)-1-((2S)-2-((3S)-3-[(2-naphthylsulfonyl)amino]-2-oxopyrrolidin-1-yl)propanoyl)piperidin-3-ylcarbamate

- 5 Using benzyl (3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate and the synthetic procedure described for Examples 403 and 404, the title compounds were prepared.

Example 405

- 10 Mass spectrum: Found: MH^+ 445
H.p.l.c. (1) Rt 2.55min

Example 406

- Mass spectrum: Found: MH^- 577
15 H.p.l.c. (1) Rt 3.37min

Example 407

tert-Butyl (1R,5S)-7-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

- 20 Using (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid and 3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid, 1,1-dimethylethyl ester* and the synthetic procedure described in Example 1, the title compound was prepared.

Mass spectrum: Found: MH^+ 605

H.p.l.c. (1) Rt 3.44min

- 25 * Reference for 3,7-Diazabicyclo[3.3.1]nonane-3-carboxylic acid, 1,1-dimethylethyl ester:
Alstermark, C; Andersson, K; Bjore, A; Bjorsne, M; Lindstedt, A.E; Nilsson, G; Polla, M; Strandlund, G; Ortengren, Y. PCT Int. Appl. (2000), WO 0077000.

Example 408

- 30 6-Chloro-N-((3S)-1-((1S)-2-[(1R,5S)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

A mixture of Example 407 (0.199g) and trifluoroacetic acid (2ml) in DCM (6ml) was stirred at room temperature for 2h and then concentrated under reduced pressure to give an oil. Saturated aqueous sodium bicarbonate (10ml) was added and the resultant mixture
35 extracted with DCM. The combined organic extracts were dried (over magnesium sulphate) and concentrated under reduced pressure to give the title compound (0.173g) as a light brown foam.

Mass spectrum: Found: MH^+ 505

H.p.l.c. (1) Rt 2.60min

Example 409

N1-[(1R,5S)-7-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]-3-(N,N-dimethylglycyl)-3,7-diazabicyclo[3.3.1]non-2-yl]-N1-[(1S,5R)-7-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonamide

- 5 A mixture of N,N-dimethylglycine (0.0062g), HOBT (0.0088g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.0124g) and N,N-di-isopropylethylamine (0.0215ml) in dry DMF (0.05ml) was sonicated for 2min. A solution of compound of Example 408 (0.025g) in dry DMF (0.2ml) was added and the resultant mixture sonicated for a further 2min. The mixture was then stirred at room temperature for 18h and concentrated under
 10 reduced pressure to give a gum-like residue, which was purified using mass directed preparative h.p.l.c. to give the title compound (0.02g) as an oil.

Mass spectrum: Found: MH^+ 590

H.p.l.c. (1) Rt 2.57min

15 Example 410

2-[(1R,5S)-7-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]-3,7-diazabicyclo[3.3.1]non-3-yl]-N,N,N-trimethyl-2-oxoethanaminium chloride

Using Example 408 and betaine hydrochloride, and the synthetic procedure described for Example 409, the title compound was prepared.

- 20 Mass spectrum: Found: MH^+ 604

H.p.l.c. (1) Rt 2.57min

Example 411

6-Chloro-N-((3S)-1-[(1S)-2-[(1R,5S)-3-(N-methylglycyl)-7-diazabicyclo[3.3.1]non-3-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide

- 25 Intermediate 99 (0.029g) was dissolved in DCM (1.5ml) and treated with trifluoroacetic acid (0.5ml). The resultant mixture was stirred at room temperature for 1.5h and then concentrated under reduced pressure. The residue was treated with saturated aqueous sodium bicarbonate (5ml) and extracted with DCM. The combined organic extracts were
 30 dried (over magnesium sulphate), filtered and concentrated under reduced pressure to give the title compound (0.026g) as a gum.

Mass spectrum: Found: MH^+ 576

H.p.l.c. (1) Rt 2.61min

35 Example 412

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-((3S)-1-[(1S)-2-[(1R,5S)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinamide formate

- A mixture of Example 407 (0.0124g), potassium carbonate (0.009g) and 2-bromoacetamide (0.0029g) in dry DMF (0.21ml) was stirred at room temperature for 19h, and then additional
 40 2-bromoacetamide (0.0015g) was added. After stirring for a further 5h, the mixture was

quenched with water (2ml), extracted with ethyl acetate, dried (over magnesium sulphate) and filtered. The combined organic extracts were concentrated under reduced pressure to give an oil which was treated with trifluoroacetic acid-DCM (2ml; 1:1), and stirred at room temperature for 5h. The mixture was concentrated under reduced pressure and the residue
 5 purified using mass directed preparative h.p.l.c. to give the title compound (0.004g) as an oil.

Mass spectrum: Found: MH^+ 562

H.p.l.c. (1) Rt 2.45min

10 Example 413

6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-((1R,5S)-7-[2-(methylamino)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide

A mixture of Example 408 (0.0198g), N-(2-chloroethyl)-N-methylamine hydrochloride (0.076g) and sodium bicarbonate (0.1g) in ethanol (0.45ml) was heated at 80 °C for 20h.

15 The cooled reaction mixture was diluted with brine, extracted with DCM, dried (over magnesium sulphate) and concentrated under reduced pressure. The resultant residue was purified using mass directed preparative h.p.l.c. to give the title compound (0.008g) as a clear gum.

Mass spectrum: Found: MH^+ 562

20 H.p.l.c. (1) Rt 2.29min

Example 414

6-Chloro-N-[2-(dimethylamino)ethyl]-N-[(3S)-1-((1S)-2-((1R,5S)-7-[2-(dimethylamino)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl)-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-

25 sulfonamide

Using Example 408 and N,N-dimethylaminoethyl chloride hydrochloride, and the synthetic procedure described for Example 413, the title compound was prepared.

Mass spectrum: Found: MH^+ 647

H.p.l.c. (1) Rt 2.33min

30

Example 415

6-Chloro-N-((3S)-1-((1S)-1-methyl-2-((1R,5S)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide trifluoroacetate

A mixture of 9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid, 1,1-dimethylethyl ester*
 35 (0.0178g), (2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid (0.037g), HOBt (0.0136g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.0194g) and N,N-di-isopropylethylamine (0.041ml) in dry DMF (0.3ml) was stirred at room temperature for 5 days and then concentrated under reduced pressure. The resultant residue was diluted with aqueous sodium hydroxide (0.5M, 5ml) and extracted with
 40 ethyl acetate. The combined organic extracts were concentrated under reduced pressure

and the residue purified using preparative thin layer chromatography (20cm x 20cm 1mm thick Whatman PKF₂₅₆ SiO₂ plate, eluting with ethyl acetate). The resultant material (0.0012g) was treated with 10% trifluoroacetic acid-DCM (10ml) at room temperature for 3h and concentrated under reduced pressure to give the title compound (0.0011g) as an oil.

5 Mass spectrum: Found: MH⁺ 507

H.p.l.c. (1) Rt 2.52min

* The corresponding HCl salt (9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid, 1,1-dimethylethyl ester, monohydrochloride) has been reported:

10 Bjoere, A; Bjoersne, M; Cladingboel, D; Hoffman, K; Pavey, J; Ponten, F; Strandlund, G; Svensson, P; Thomson, C; Wilstermann, M. PCT Int. Appl. (2001), WO 0128992.

Example 416

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperazin-1-ylethyl]-2-

15 oxopyrrolidin-3-yl}glycinamide trifluoroacetate

Using (2S)-2-((3S)-3-((2-amino-2-oxoethyl)[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoic acid and 1-Boc-piperazine, and the synthetic procedure described for Example 1, provided the Intermediate t-butyl ester. This was subsequently deprotected using trifluoroacetic acid to provide the title compound.

20 Mass spectrum: Found: MH⁺ 522

H.p.l.c. (1) Rt 2.39min

Example 417

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-1,4-diazepan-1-yl)-

25 2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide formate

Using Intermediate 49 and the procedure described for Example 1, the title compound was prepared.

Mass spectrum: Found: MH⁺ 550

H.p.l.c. (1) Rt 2.45min

30 Using similar chemistry, the following were prepared:

Example 418

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-
1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide

35 Mass spectrum: Found: MH⁺ 551

H.p.l.c. (1) Rt 3.02min

Example 419

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-[(1S,4S)-2-oxa-5-

40 azabicyclo[2.2.1]hept-5-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide

Mass spectrum: Found: MH^+ 535

H.p.l.c. (1) Rt 2.83min

Example 420 and Example 421

- 5 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide [Isomer 1 and Isomer 2]

Isomer 1

Mass spectrum: Found: MH^+ 585

H.p.l.c. (1) Rt 2.61min

- 10 Isomer 2

Mass spectrum: Found: MH^+ 585

H.p.l.c. (1) Rt 2.62min

Example 422

- 15 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide

Mass spectrum: Found: MH^+ 564

H.p.l.c. (1) Rt 2.70min

- 20 Example 423 and Example 424

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide [Isomer 1 and Isomer 2]

Isomer 1

Mass spectrum: Found: MH^+ 584

- 25 H.p.l.c. (1) Rt 2.70min

Isomer 2

Mass spectrum: Found: MH^+ 584

H.p.l.c. (1) Rt 2.73min

- 30 Example 425

N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-[2-(4-methylpyridin-2-yl)pyrrolidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide

Mass spectrum: Found: MH^+ 599

H.p.l.c. (1) Rt 2.8min

- 35

Example 426

(E)-2-(3-Chloro-4-hydroxyphenyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethanesulfonamide

- 40 Sulphuryl chloride (0.036ml) was added dropwise to DMF (0.04ml) at 0 °C and the mixture was stirred at room temperature for 2h. Intermediate 105 (0.102g) in cyclohexane (0.2ml)

was added in one portion and the resultant mixture was heated at 90 °C for 6h. The cooled reaction mixture was poured onto ice and extracted with DCM. The combined organic extracts were dried (over magnesium sulphate) and concentrated under reduced pressure to give a brown oil which was treated with sulphuryl chloride (0.035ml) and triphenyl phosphine (0.103g) in dry DCM (ca. 0.5ml). After stirring for 3h at room temperature, the mixture was filtered through a SPE silica cartridge preconditioned with cyclohexane. Elution with ethyl acetate gave, after concentration under reduced pressure, an orange-brown solid which was stirred with Intermediate 87 (0.04g), 4-dimethylaminopyridine (0.021g), diisopropylethylamine (0.059ml) in dry DCM (1ml). After stirring for 3 days at room temperature under nitrogen, the mixture was concentrated under reduced pressure. The residue was purified initially using SPE (silica) followed by mass directed preparative h.p.l.c. to give the title compound (0.0035g) as a white solid.

Mass spectrum: Found: MH^+ 458

H.p.l.c. (1) Rt 2.58min

Example 427

(E)-2-(4-Chloro-3-hydroxyphenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

To a solution of (E)-2-(3-[[*tert*-butyl(diphenyl)silyl]oxy]-4-chlorophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide (0.0078g) in THF (0.3ml) at -78°C under nitrogen, tetra n-butylammonium fluoride (1M in THF, 0.014ml) was added. The mixture was allowed to warm to room temperature over 3 days and then concentrated under reduced pressure. The residue was purified using mass directed preparative h.p.l.c. to give the title compound (0.0043g) as a clear film.

Mass spectrum: Found: MH^+ 458

H.p.l.c. (1) Rt 2.67min

Example 428

6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-N-(2-morpholin-4-ylethyl)naphthalene-2-sulfonamide formate

Example 1 (0.05g) was dissolved in DMF (1ml) and treated with chloroethylmorpholine hydrochloride (0.062g) and potassium carbonate (0.093g), and stirred at 40°C for 2h. The mixture was then heated at 80°C for 8h, cooled and treated with ethyl acetate and water. The organic extract was dried (over magnesium sulphate) and concentrated under reduced pressure. The residue was purified using mass directed preparative h.p.l.c. to give the title compound (0.018g) as a white solid.

Mass spectrum: Found: MH^+ 579

H.p.l.c. (1) Rt 2.56min

Using similar chemistry, the following were prepared:

Example 429

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-pyrrolidin-1-ylethyl)naphthalene-2-sulfonamide formate

Mass spectrum: Found: MH^+ 563

5 H.p.l.c. (1) Rt 2.58min

Example 430

6-Chloro-N-[2-(dimethylamino)ethyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate

10 Mass spectrum: Found: MH^+ 537

H.p.l.c. (1) Rt 2.53min

Example 431

15 N-[2-[(6-Chloro-2-naphthyl)sulfonyl][(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]amino)ethyl]acetamide

Mass spectrum: Found: MH^+ 551

H.p.l.c. (1) Rt 2.91min

Example 432

20 6-Chloro-N-[2-oxo-1-[1-(piperidin-1-ylcarbonyl)propyl]pyrrolidin-3-yl]naphthalene-2-sulfonamide [Isomer 1 and Isomer 2]

Using 2-(3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)butanoic acid [Isomer 1 and Isomer 2] and the synthetic procedure described for Example 1, the title compound was prepared.

25 Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.37min

Using similar chemistry, the following was prepared:

Example 433

30 6-Chloro-N-[2-oxo-1-[1-(pyrrolidin-1-ylcarbonyl)propyl]pyrrolidin-3-yl]naphthalene-2-sulfonamide [Isomer 1 and Isomer 2]

Mass spectrum: Found: MH^+ 464

H.p.l.c. (1) Rt 3.21min

35 Example 434

6-Chloro-N-[1-(1-[(2S)-2-methylpiperidin-1-yl]carbonyl)propyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide [Isomer 3 and Isomer 4]

Using 2-(3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)butanoic acid [Isomer 3 and Isomer 4] and the synthetic procedure described for Example 1, the title compound

40 was prepared.

Mass spectrum: Found: MH^+ 492

H.p.l.c. (1) Rt 3.13min

Using similar chemistry, the following was prepared:

5 Example 435

6-Chloro-N-{2-oxo-1-[1-(piperidin-1-ylcarbonyl)propyl]pyrrolidin-3-yl}naphthalene-2-sulfonamide [Isomer 3 and Isomer 4]

Mass spectrum: Found: MH^+ 478

H.p.l.c. (1) Rt 3.12min

10

Example 436

6-Chloro-N-((3R)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate

Using Intermediate 31 and the procedure described for Example 1, the title compound was prepared.

15

Mass spectrum: Found: MH^+ 533

H.p.l.c. (1) Rt 2.63min

Example 437

20 5-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-1H-indole-2-sulfonamide

Intermediate 64 (0.011g) was dissolved in 1:1 TFA / DCM (0.5ml) and allowed to stand at room temperature for 1h. The mixture was concentrated under reduced pressure and the residue solvents partitioned between saturated aqueous sodium bicarbonate and DCM. The separated organic phase was dried (over magnesium sulphate) and concentrated under a stream of nitrogen to give the title compound (0.0082g) as white solid.

25

Mass spectrum: Found: MH^+ 455

H.p.l.c. (1) Rt 2.97min

30 Example 438

6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-1,3-benzothiazole-2-sulfonamide

Intermediate 66 (0.1g) was stirred at room temperature in anhydrous acetone (3ml) and 5% aqueous potassium permanganate (1.35ml) for 3h, after which additional acetone (3ml) and 5% aqueous potassium permanganate (1.35ml) were added. The reaction mixture was stirred for a further 18h and filtered through CeliteTM. The filtrate was concentrated under reduced pressure and the residue purified by mass directed preparative h.p.l.c to give the title compound (0.0062g) as a white solid.

35

Mass spectrum: Found: MH^+ 473

40 H.p.l.c. (1) Rt 2.98min

Example 439

1-(3-Cyanophenyl)-N-{(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}methanesulfonamide

5 The title compound was prepared using Intermediate 23 and (3-cyanophenyl)methanesulfonyl chloride, and the synthetic procedure described for Example 386 (Route 1).

Mass spectrum: Found: MH^+ 419

H.p.l.c. (1) Rt min

10

Example 440

5-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}thieno[2,3-b]pyridine-2-sulfonamide

15 The title compound was prepared using Intermediates 57 and 87, and the synthetic procedure described for Example 386 (Route 1).

Mass spectrum: Found: MH^+ 473

H.p.l.c. (1) Rt 2.64min

Example 441

20 5-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}thieno[3,2-b]pyridine-2-sulfonamide

The title compound was prepared using Intermediates 87 and 118, and the synthetic procedure described for Example 386 (Route 1).

Mass spectrum: Found: MH^+ 473

25 H.p.l.c. (1) Rt 2.53min

Example 442

6-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2-oxopyrrolidinyl}thieno[3,2-b]pyridine-2-sulfonamide

30 The title compound was similarly prepared using Intermediate 87 and 6-chlorothieno[3,2-b]pyridine-2-sulfonyl chloride*, and the synthetic procedure described for Example 386 (Route 1).

Mass spectrum: Found: MH^+ 473

H.p.l.c. (I) Rt 2.61min

35

*Prepared according to the procedure described in US6281227.

Example 443

40 (E)-2-(5-Chlorothien-2-yl)-N-methyl-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide

Sodium hydride (60% dispersion in oil, 0.011g) was added to trimethylsulphonium iodide (0.059g) in dimethylsulphoxide (2ml) between 5-10°C, and the resultant mixture was stirred at room temperature for 30min. Example 386 (0.1g) in dry THF (2ml) was added between 5-10°C, and the solution stirred at room temperature for 2.25h, at 50°C for 70h, cooled to room temperature and poured onto ice/water. The aqueous mixture was extracted with ethyl acetate and the combined, dried (over magnesium sulphate) organic extracts were concentrated under reduced pressure. The residue was purified using mass directed preparative h.p.l.c. to give the title compound (0.038g) as a colourless oil.

Mass spectrum: Found: MH^+ 462

10 H.p.l.c. (1) Rt 2.82min

15

In vitro assay for inhibition of Factor Xa

Compounds of the present invention were tested for their Factor Xa inhibitory activity as determined *in vitro* by their ability to inhibit human Factor Xa in a chromogenic assay, using N- α -benzyloxycarbonyl-D-Arg-Gly-Arg-p-nitroanilide as the chromogenic substrate.

20 Compounds were diluted from a 10mM stock solution in dimethylsulfoxide at appropriate concentrations. Assay was performed at room temperature using buffer consisting of: 50mM Tris-HCl, 150mM NaCl, 5mM CaCl₂, pH 7.4. containing human Factor Xa (final conc. Of 0.0015 U.ml⁻¹). Compound and enzyme were preincubated for 15min prior to addition of the substrate (final conc. of 200 μ M). The reaction was stopped after 30min with the addition of
25 soybean trypsin inhibitor or H-D-PHE-PRO-ARG-Chloromethylketone. BioTek EL340 or Tecan SpectraFluor Plus plate readers were used to monitor the absorbance at 405nm. To obtain IC₅₀ values the data were analysed using ActivityBase® and XLfit®.

All of the synthetic Example compounds tested exhibited measurable FXa inhibitory activity.

30 Preferably compounds have an IC₅₀ value of less than 2 μ M, more preferably compounds have an IC₅₀ value of less than 0.1 μ M.

Measurement of prothrombin time (PT) – Test 1

35 Blood was collected into a sodium citrate solution (ratio 9:1) to give a final concentration of 0.38% citrate. Plasma was generated by centrifugation of citrated blood samples at 1200 xg for 20min at 4°C .

The PT test was performed at 37°C in plastic cuvettes containing a magnetic ball bearing. 50 μ L of citrated plasma and either 25 μ L of 2.8% DMSO for control or 25 μ L of test compound
40 (dissolved in DMSO and diluted in water and 2.8% DMSO to give 0.4% DMSO final in

assay) at a concentration of 7-times the final desired concentration was pipetted into each cuvette. This mixture was incubated for 1min at 37°C before adding 100µL of thromboplastin mixture (comprising lyophilised rabbit thromboplastin and calcium chloride which was reconstituted in distilled water as per manufacturer's [Sigma] instructions). On addition of the thromboplastin mixture, the timer was automatically started and continued until the plasma clotted. The time to clotting was recorded (normal range for human plasma is 10-13 seconds).

Method for measurement of prothrombin time (PT) – Test 2

- 10 Blood is collected into a sodium citrate solution (ratio 9:1) to give a final concentration of 0.38% citrate. Plasma is generated by centrifugation of citrated blood samples at 1200 xg for 20min at 4°C.

The PT test is performed at 37°C in plastic cassettes and using a MCA210 Microsample Coagulation Analyzer (Bio/Data Corporation). For assay, 25 ul of plasma containing test compound at concentrations ranging from 0.1 to 100 uM (made from a 1 mM stock solution in 10% DMSO and plasma) and 25 ul of Thromboplastin C Plus (Dade Berhing) are automatically injected into the cassette. Upon addition of the Thromboplastin C Plus, the instrument determines and records the time to clot (normal range for human plasma is 10-13 seconds).

General purification and analytical methods

Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3µm, 3.3cm x 4.6mm ID) eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 95% acetonitrile and 0.05% HCO₂H in water (solvent B), using the following elution gradient 0-0.7 minutes 0%B, 0.7-4.2 minutes 0→100%B, 4.2-5.3 minutes 100%B, 5.3-5.5 minutes 100→0%B at a flow rate of 3 ml/minutes (System 1). The mass spectra (MS) were recorded on a Fisons VG Platform mass spectrometer using electrospray positive ionisation [(ES+ve to give MH⁺ and M(NH₄)⁺ molecular ions] or electrospray negative ionisation [(ES-ve to give (M-H)⁻ molecular ion] modes.

¹H nmr spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the external standard.

BiotageTM chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KPSil.

35 Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (5cm x 10mm i.d.) with 0.1% HCO₂H in water and 95% MeCN, 5% water (0.5% HCO₂H) utilising the following gradient elution conditions: 0-1.0 minutes 5%B, 1.0-8.0 minutes 5→30%B, 8.0-8.9 minutes 30%B, 8.9-9.0 minutes 30→95%B, 9.0-9.9 minutes 95%B, 9.9-10 minutes 95→0%B at a

flow rate of 8ml minutes⁻¹ (System 2). The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

Hydrpophobic frits refers to filtration tubes sold by Whatman.

SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent
5 Technology Ltd.

TLC (thin layer chromatography) refers to the use of TLC plates sold by Merck coated with silica gel 60 F₂₅₄.

10 LC/MS System (3)

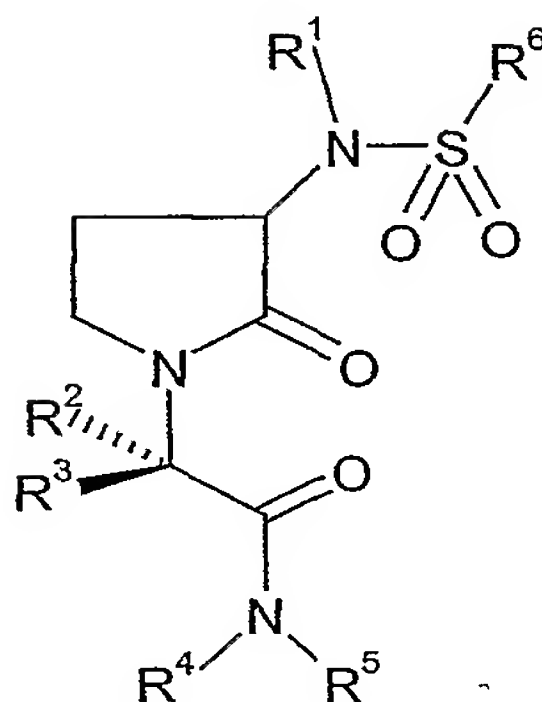
Method 2 was conducted on a Waters Xtera RP18 column (3µm, 15cm x 2.1mm ID) eluting with solvent A (0.1% HCO₂H and water) and solvent B (100% acetonitrile, 0.1% HCO₂H and reserpine 2.5µgml⁻¹) at 20°C. The following elution gradient was ran: 0-2.0 minutes 0% B; 2.0-18.0 minutes 0-100% B; 18.0-20.0 minutes 100%B; 20.0-22.0 minutes 100-0%B;
15 22.0-30.0 minutes 0%B, at a flow rate of 0.4 ml/minutes. The mass spectra (MS) were recorded on a Micromass QTOF 2 spectrometer using electrospray positive ionisation [ES+ve to give MH⁺].

Note: The number given in brackets in the Examples and Intermediates above, e.g. H.p.l.c.

20 (1), specifies the LC/MS method used.

Claims

1. A compound of formula (Ic):



5

(Ic)

wherein:

R¹ represents hydrogen, -C₁₋₆alkyl, -C₃₋₆alkenyl, -C₃₋₆alkynyl, -C₂₋₃alkylOH, -C₂₋₃alkylNR^bR^a, -C₂₋₃alkylNHCOR^a, -C₂₋₃alkylNHCO₂R^b, -C₂₋₃alkylNHSO₂R^b, -C₂₋₃alkylNHCONR^bR^c, -C₂₋₃alkyl
 10 OCONR^bR^c, -C₂₋₃alkylOC₁₋₆alkyl, -C₂₋₃alkylOCH₂phenyl, phenyl or 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH, or R¹ represents a group X-W;

15 X represents -C₁₋₃alkylene-, propenylene, propynylene;

W represents -CN, -CO₂H, -CONR^bR^c, -COC₁₋₆alkyl, -CO₂C₁₋₆alkyl, -CO₂C₃₋₆alkenyl, phenyl or 5- or 6- membered aromatic or non-aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic or non-aromatic heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;
 20

R^a represents hydrogen, -C₁₋₃alkyl, phenyl or a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;
 25

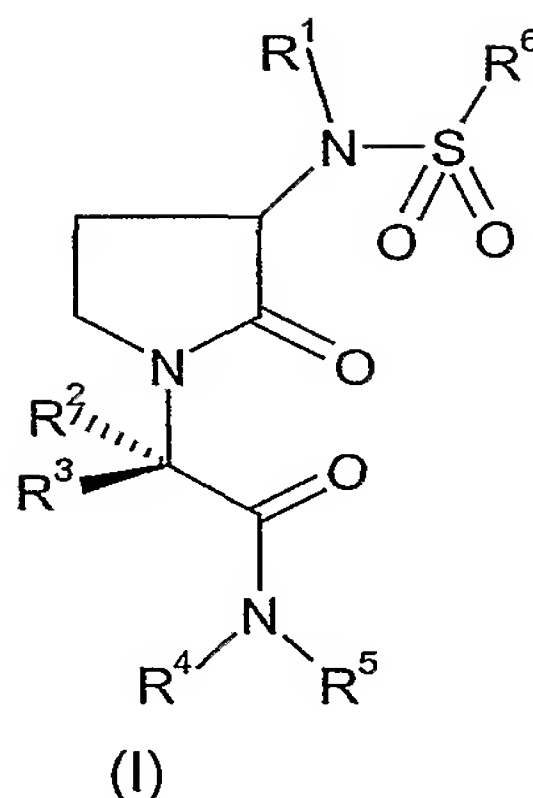
R^b and R^c independently represent hydrogen or -C₁₋₄alkyl;

R² and R³ independently represent hydrogen, -C₁₋₃alkyl or -CF₃, with the proviso that one of
 30 R² and R³ is -C₁₋₃alkyl or -CF₃ and the other is hydrogen;

R⁴ and R⁵, together with the N atom to which they are bonded, form a 4-, 5-, 6-, 7- or 8-membered non-aromatic heterocyclic ring, bridged or unbridged, optionally containing an additional heteroatom selected from O, N or S, and optionally substituted by:

- 5 (i) one or more substituents selected from: -NH₂, -CF₃, F, -OH, =O, -CO₂H, -C₁₋₆alkyl, -C₁₋₆alkoxy, -C₁₋₆alkylOH, -(C₁₋₃alkyl)NR^bR^c, -(C₀₋₃alkyl)CONR^bR^c, -NHSO₂CF₃, -NHSO₂(C₀₋₃alkyl)R^a, -NHCH₂COCH₂O(C₁₋₃alkyl), -(C₀₋₃alkyl)CO₂C₁₋₄alkyl, -CONHC₂₋₃alkylOH, -CH₂NHC₂₋₃alkylOH, -CH₂OC₁₋₃alkyl, -COCH₂NR^bR^c, -COCH₂N⁺(CH₃)₃ and -CH₂SO₂C₁₋₃alkyl;
- (ii) a group -NHCOR^d or -NR^bR^d;
- 10 R^d represents -C₁₋₆alkyl, -C₂₋₆alkynyl, -C₁₋₆alkoxy, -C₁₋₆alkylOH, -C₁₋₃alkylCO₂H, -C₁₋₃alkylNR^bR^c, -C₁₋₃alkylCO₂C₁₋₃alkyl, -C₁₋₃alkylCONR^bR^c and -C₁₋₃alkylOC₁₋₃alkyl;
- (iii) a group -Y-R^e;
- Y represents -C₁₋₃alkylene-, -NHCO-, -NHCO₂C₁₋₃alkylene-, -NHC₁₋₃alkylene-, -CO-, -C₁₋₃alkylNH-, -C₁₋₃alkylNHCO-, -C₁₋₃alkylNHSO₂-, -CH₂NHSO₂CH₂- or a direct link;
- 15 R^e represents phenyl, phenyl, a 5- or 6- membered heterocycle containing at least one heteroatom selected from O, N or S, or a 5- or 6- membered cycloalkyl, each of which is optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH; or
- (iv) a second ring R^f which is fused to the non-aromatic heterocyclic ring formed by R⁴ and R⁵,
- 20 R^f, wherein R^f represents phenyl, a 5- or 6- membered cycloalkyl group or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, and the fused bicyclic group is optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, -C₁₋₃alkylOH, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;
- 25 with the proviso that where the substituent on the non-aromatic ring formed by R⁴ and R⁵ is -NH₂, -OH, -C₁₋₆alkoxy, -NHSO₂CF₃, -NHSO₂(C₀₋₃alkyl)R^a, -NHCOR^d, -NR^bR^d, -NHCOR^e, -NHCO₂C₁₋₃alkyleneR^e or -NHC₁₋₃alkyleneR^e, -NHCH₂COCH₂O(C₁₋₃alkyl), the substituent is not attached to a ring carbon atom adjacent to a heteroatom;
- R⁶ represents:
- 30 (i) a fused bicyclic group -R^gR^h;
- (ii) a group -R^g-R^h;
- (iii) a group -Z-R^h wherein Z represents -C₁₋₃alkylene-, -C₂₋₃alkenylene- or a direct link;
- wherein R^g and R^h independently represent phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or
- 35 aromatic heterocyclic group being optionally substituted by one or more substituents selected from: -C₁₋₃alkyl, -C₁₋₃alkoxy, halogen, -CN, -CF₃, -NH₂, -CO₂H and -OH;
- and pharmaceutically acceptable derivatives thereof.

2. A compound of formula (I)



5

wherein:

R^1 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{2-3}$ alkylOH, $-C_{2-3}$ alkylNR^bR^a, $-C_{2-3}$ alkylNHCOR^a, $-C_{2-3}$ alkylNHCO₂R^b, $-C_{2-3}$ alkylNHSO₂R^b, $-C_{2-3}$ alkylNHCONR^bR^c or a group
10 X-W;

X represents $-C_{1-3}$ alkylene-, propenylene, propynylene;

W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl, $-CO_2C_{2-6}$ alkenyl, $-OCONR^bR^c$, $-OC_{1-6}$ alkyl, $-OCH_2$ phenyl, phenyl or 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or aromatic
15 heterocyclic group being optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-C_{1-3}$ alkylOH, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

R^a represents hydrogen, $-C_{1-3}$ alkyl, phenyl or a 5- or 6- membered heterocyclic group containing at least one heteroatom selected from O, N or S, the phenyl or heterocyclic group
20 being optionally substituted by one or more substituents selected from: $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-C_{1-3}$ alkylOH, halogen, $-CN$, $-CF_3$, $-NH_2$, $-CO_2H$ and $-OH$;

R^b and R^c independently represent hydrogen or $-C_{1-3}$ alkyl;

25 R^2 and R^3 independently represent hydrogen, $-C_{1-3}$ alkyl or $-CF_3$, with the proviso that when one of R^2 and R^3 is $-C_{1-3}$ alkyl or $-CF_3$, the other is hydrogen;

R^4 and R^5 , together with the N atom to which they are bonded, form a 5-, 6- or 7- membered non-aromatic heterocyclic ring, bridged or unbridged, optionally containing an additional
30 heteroatom selected from O, N or S, and optionally substituted by: (i) one or more

substituents selected from: -NH_2 , -CF_3 , F , -OH , =O , $\text{-CO}_2\text{H}$, $\text{-C}_{1-6}\text{alkyl}$, $\text{-C}_{1-6}\text{alkoxy}$, $\text{-C}_{1-6}\text{alkylOH}$, $\text{-(C}_{1-3}\text{alkyl)NR}^b\text{R}^c$, $\text{-(C}_{0-3}\text{alkyl)CONR}^b\text{R}^c$, $\text{-NHSO}_2\text{CF}_3$, $\text{-NHSO}_2(\text{C}_{0-3}\text{alkyl})\text{R}^a$ and $(\text{C}_{0-3}\text{alkyl})\text{CO}_2\text{C}_{1-3}\text{alkyl}$;

(ii) a group -NHCOR^d or $\text{-NR}^b\text{R}^d$,

5 R^d represents $\text{-C}_{1-6}\text{alkyl}$, $\text{-C}_{2-6}\text{alkynyl}$, $\text{-C}_{1-6}\text{alkoxy}$, $\text{-C}_{1-6}\text{alkylOH}$, $\text{-C}_{1-3}\text{alkylCO}_2\text{H}$, $\text{-C}_{1-3}\text{alkylNR}^b\text{R}^c$, $\text{-C}_{1-3}\text{alkylCO}_2\text{C}_{1-3}\text{alkyl}$ or $\text{-C}_{1-3}\text{alkylCONR}^b\text{R}^c$;

(iii) a group -Y-R^e ,

Y represents $\text{-C}_{1-3}\text{alkylene-}$, -NHCO- , $\text{-NHCO}_2\text{C}_{1-3}\text{alkylene-}$, $\text{-NHC}_{1-3}\text{alkylene-}$, -CO- , $\text{-C}_{1-3}\text{alkylNH-}$, $\text{-C}_{1-3}\text{alkylNHCO-}$, $\text{-C}_{1-3}\text{alkylNHSO}_2\text{-}$, $\text{-CH}_2\text{NHSO}_2\text{CH}_2\text{-}$ or a direct link,

10 R^e represents phenyl, a 5- or 6- membered cycloalkyl or a 5- or 6- membered heterocycle containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by one or more substituents selected from: $\text{-C}_{1-3}\text{alkyl}$, $\text{-C}_{1-3}\text{alkoxy}$, $\text{-C}_{1-3}\text{alkylOH}$, halogen, -CN , -CF_3 , -NH_2 , $\text{-CO}_2\text{H}$ and -OH or

(iv) a second ring R^f which is fused to the non-aromatic heterocyclic ring formed by R^4

15 and R^5 , wherein R^f represents phenyl, a 5- or 6- membered cycloalkyl group or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, and the fused bicyclic group is optionally substituted by one or more substituents selected from: $\text{-C}_{1-3}\text{alkyl}$, $\text{-C}_{1-3}\text{alkoxy}$, $\text{-C}_{1-3}\text{alkylOH}$, halogen, -CN , -CF_3 , -NH_2 , $\text{-CO}_2\text{H}$ and -OH ;

20 with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is -NH_2 , -OH , $\text{-C}_{1-6}\text{alkoxy}$, $\text{-NHSO}_2\text{CF}_3$, $\text{-NHSO}_2(\text{C}_{0-3}\text{alkyl})\text{R}^a$, -NHCOR^d , $\text{-NR}^b\text{R}^d$, -NHCOR^e , $\text{-NHCO}_2\text{C}_{1-3}\text{alkyleneR}^e$ or $\text{-NHC}_{1-3}\text{alkyleneR}^e$, the substituent is not attached to a ring carbon atom adjacent to a heteroatom;

25 R^6 represents:

(i) a fused bicyclic group $\text{-R}^g\text{R}^h$;

(ii) a group $\text{-R}^g\text{-R}^h$;

(iii) a group -Z-R^h wherein Z represents $\text{-C}_{1-3}\text{alkylene-}$, $\text{-C}_{2-3}\text{alkenylene-}$ or a direct link;

wherein R^g and R^h independently represent phenyl or a 5- or 6- membered aromatic

30 heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by one or more substituents selected from: $\text{-C}_{1-3}\text{alkyl}$, $\text{-C}_{1-3}\text{alkoxy}$, halogen, -CN , -CF_3 , -NH_2 , $\text{-CO}_2\text{H}$ and -OH ;

and pharmaceutically acceptable salts or solvates thereof.

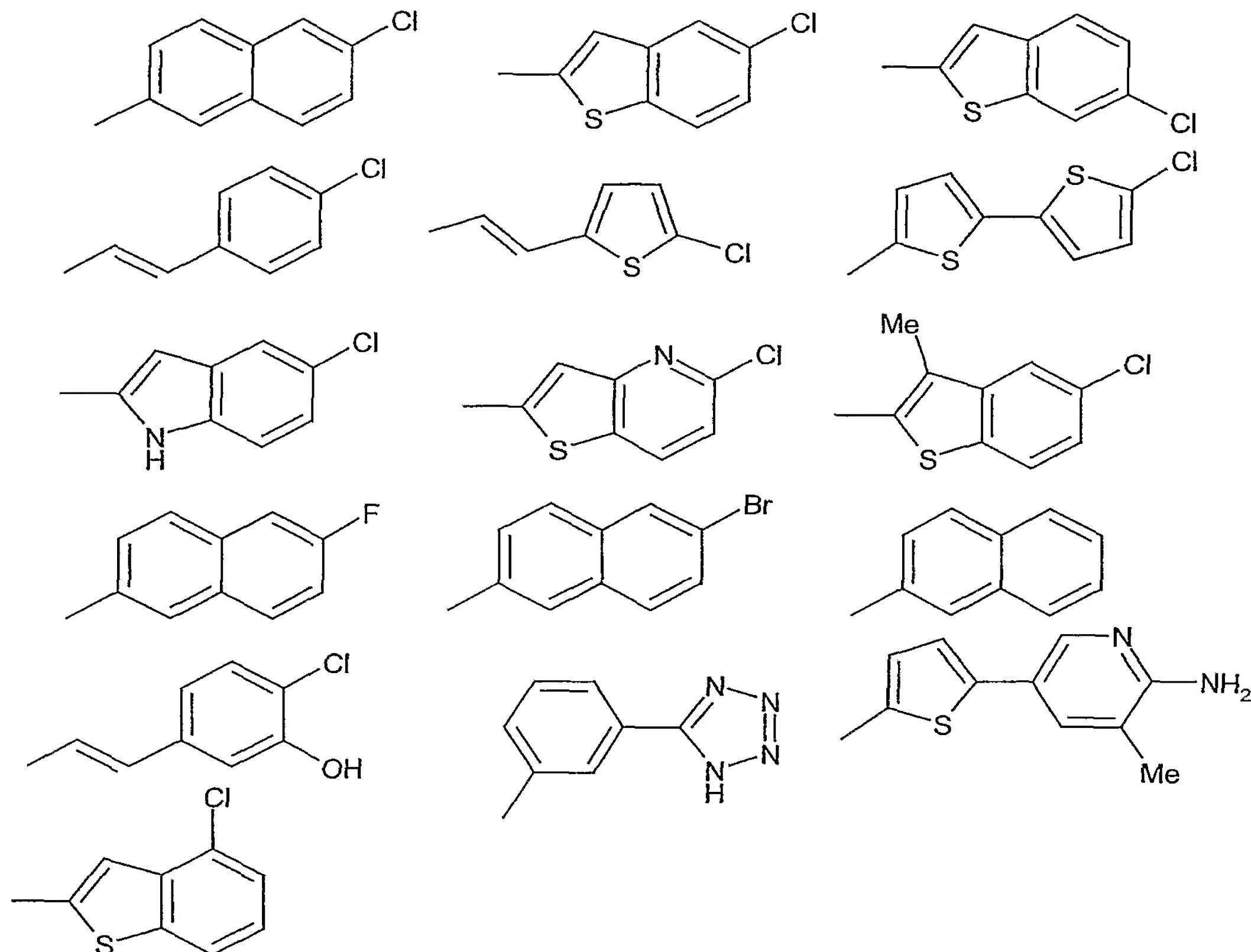
35 3. A compound as claimed in claim 1 or claim 2 wherein R^1 represents hydrogen, $\text{-C}_{1-6}\text{alkyl}$, $\text{-C}_{2-6}\text{alkenyl}$ or a group X-W wherein X represents $\text{-C}_{1-3}\text{alkylene-}$ and W represents -CN , $\text{-CO}_2\text{H}$, $\text{-CONR}^b\text{R}^c$, $\text{-COC}_{1-6}\text{alkyl}$, $\text{-CO}_2\text{C}_{1-6}\text{alkyl}$ or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S.

4. A compound as claimed in claim 1 wherein R^1 represents hydrogen, $-C_{1-6}$ alkyl, $-C_{3-6}$ alkenyl, $-C_{2-3}$ alkyl NR^bR^a , $-C_{2-3}$ alkyl $NHCOR^a$, phenyl or a 5- or 6- membered aromatic heterocycle, or R^1 represents a group X-W wherein X represents $-C_{1-3}$ alkylene- and W represents $-CN$, $-CO_2H$, $-CONR^bR^c$, $-COC_{1-6}$ alkyl, $-CO_2C_{1-6}$ alkyl or a 5- or 6- membered aromatic or non-aromatic heterocyclic group containing at least one heteroatom selected from O, N or S.
5. A compound as claimed in any one of claims 1-4 wherein R^2 represents $-C_{1-3}$ alkyl or hydrogen.
6. A compound as claimed in any one of claims 1-5 wherein R^3 represents $-C_{1-3}$ alkyl or hydrogen.
7. A compound as claimed in any one of claims 1-6 wherein R^4 and R^5 , together with the N atom to which they are bonded, form a 5- or 6- membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom selected from O, N or S, and optionally substituted by:
- (i) one or more substituents selected from: $-NH_2$, $-CF_3$, $-OH$, $-CO_2H$, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-C_{1-6}$ alkylOH, $-(C_{1-3}alkyl)NR^bR^c$, $-(C_{0-3}alkyl)CONR^bR^c$ and $-NHSO_2CF_3$;
 - (ii) a group $NHCOR^d$ wherein R^d represents $-C_{1-6}$ alkyl, $-C_{2-6}$ alkynyl, $-C_{1-6}$ alkoxy, $-C_{1-3}alkylCO_2H$, $-C_{1-3}alkylNR^bR^c$, $-C_{1-3}alkylCO_2C_{1-3}alkyl$ or $-C_{1-3}alkylCONR^bR^c$ or a group NHR^d wherein R^d represents $-C_{1-6}$ alkyl or $-C_{1-6}$ alkylOH;
 - (iii) a group $-Y-R^e$, Y represents $-C_{1-3}alkylene-$, $-NHCO-$, $-NHCO_2C_{1-3}alkylene-$, $-NHC_{1-3}alkylene-$ or $-C_{1-3}alkylNHSO_2-$, R^e represents imidazole, pyrrole, pyrazole, pyridine, pyrimidine, furan, oxazole, 1,2,4-triazole, phenyl or pyrrolidine optionally substituted by $-C_{1-3}alkyl$, NH_2 or $-C_{1-3}alkylOH$;
 - (iv) a second ring R^f which is fused to the non-aromatic heterocyclic ring formed by R^4 and R^5 , wherein R^f represents cyclohexyl;
- with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is $-NH_2$, $-OH$, $-C_{1-6}$ alkoxy, $-NHSO_2CF_3$, $-NHCOR^d$, $-NR^bR^d$, $-NHCOR^e$, $-NHCO_2C_{1-3}alkyleneR^e$ or $-NHC_{1-3}alkyleneR^e$, the substituent is not attached to a ring carbon atom adjacent to a heteroatom;
8. A compound as claimed in claim 1 wherein R^4 and R^5 , together with the N atom to which they are bonded, form a 4-, 5-, 6-, 7- or 8- membered non-aromatic heterocyclic ring, selected from: piperidine; pyrrolidine; hexamethyleneimine (homopiperidine); morpholine; thiomorpholine; diazepine; tetrahydro-1,6-naphthyridine; 2-azabicyclo[2.2.1]heptane; 2-oxa-5-azabicyclo[2.2.1]heptane; 3,7-diazabicyclo[3.3.1]nonane; 9-oxa-3,7-diazabicyclo[3.3.1]nonane; 2-azabicyclo[2.2.2]octane; 4,6,7,8-tetrahydro-5h-thieno[3,2-c]azepine;

1,2,5,6-tetrahydropyridine; azetidine; 2,5-dihydro-1h-pyrrole; piperazine; hexahydropyrimidine; tetrahydroquinoline; decahydroquinoline; tetrahydroquinoxaline; dihydroisoindole; tetrahydroisoquinoline; tetrahydro-5h-imidazo[4,5-c]pyridine; 1,3,4,5-tetrahydro-2h-2-benzazepine; 2,5-diazabicyclo[2.2.1]heptane; optionally substituted by:

- 5 (i) one or more substituents selected from: $-\text{NH}_2$, $-\text{CF}_3$, F , $-\text{OH}$, $=\text{O}$, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{alkoxy}$, $-\text{C}_{1-6}\text{alkylOH}$, $-(\text{C}_{1-3}\text{alkyl})\text{NR}^b\text{R}^c$, $-(\text{C}_{0-3}\text{alkyl})\text{CONR}^b\text{R}^c$, $-\text{NHSO}_2\text{CF}_3$, $-\text{NHCH}_2\text{COCH}_2\text{O}(\text{C}_{1-3}\text{alkyl})$, $-(\text{C}_{0-3}\text{alkyl})\text{CO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{CONHC}_{2-3}\text{alkylOH}$, $-\text{COCH}_2\text{NR}^b\text{R}^c$, $-\text{COCH}_2\text{N}^+(\text{CH}_3)_3$, $-\text{CH}_2\text{OC}_{1-3}\text{alkyl}$ and $-\text{CH}_2\text{SO}_2\text{C}_{1-3}\text{alkyl}$;
(ii) a group $-\text{NHCOR}^d$ or $-\text{NR}^b\text{R}^d$;
- 10 R^d represents $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{1-6}\text{alkylOH}$, $-\text{C}_{1-3}\text{alkylCO}_2\text{H}$, $-\text{C}_{1-3}\text{alkylNR}^b\text{R}^c$, $-\text{C}_{1-3}\text{alkylCO}_2\text{C}_{1-3}\text{alkyl}$, $-\text{C}_{1-3}\text{alkylOC}_{1-3}\text{alkyl}$ and $-\text{C}_{1-3}\text{alkylCONR}^b\text{R}^c$;
(iii) a group $-\text{Y-R}^e$,
 Y represents $-\text{C}_{1-3}\text{alkylene-}$, $-\text{NHCO-}$, $-\text{NHC}_{1-3}\text{alkylene-}$, $-\text{NHCO}_2\text{C}_{1-3}\text{alkylene-}$, $-\text{C}_{1-3}\text{alkylNHCO-}$, $-\text{C}_{1-3}\text{alkylNHSO}_2-$, $-\text{CO-}$ or a direct link,
- 15 R^e represents phenyl, pyridine, pyrrole, isoxazole, pyrazole, pyrrolidine, cyclopentyl, triazole, pyrazine, furan, thiazole, imidazole, morpholine, piperazine, pyrimidine, piperidine, each of which is optionally substituted by one or more substituents selected from: $-\text{C}_{1-3}\text{alkyl}$, halogen, $-\text{NH}_2$;
- with the proviso that where the substituent on the non-aromatic ring formed by R^4 and R^5 is -
- 20 NH_2 , $-\text{OH}$, $-\text{C}_{1-6}\text{alkoxy}$, $-\text{NHSO}_2\text{CF}_3$, $-\text{NHCOR}^d$, $-\text{NR}^b\text{R}^d$, $-\text{NHCOR}^e$, or $-\text{NHC}_{1-3}\text{alkyleneR}^e$, $-\text{NHCO}_2\text{C}_{1-3}\text{alkyleneR}^e$, $-\text{NHCH}_2\text{COCH}_2\text{O}(\text{C}_{1-3}\text{alkyl})$, the substituent is not attached to a ring carbon atom adjacent to a heteroatom.

9. A compound as claimed in any one of claims 1-8 wherein R⁶ represents



10. A compound as claimed in claim 1 selected from:

- 5 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide ;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[2-(2-pyrrolidin-1-ylethyl)piperidin-1-yl]ethyl]-2-
- 10 oxopyrrolidin-3-yl)naphthalene-2-sulfonamide ;
- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-(3,3-difluoropiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 15 6-Chloro-N-((3S)-1-[(1S)-2-(4,4-difluoropiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-(3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- N-((3S)-1-[(1S)-2-[(1R,4S)-2-Azabicyclo[2.2.1]hept-2-yl]-1-methyl-2-oxoethyl]-2-
- 20 oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;

- 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
 N-{1-[(1S)-2-Azepan-1-yl-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-6-chloronaphthalene-2-sulfonamide;
- 5 N-((3S)-1-[(1S)-2-(2-Azabicyclo[2.2.2]oct-2-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide;
 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)ethenesulfonamide formate;
- 10 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
 5-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
- 15 N2-[(E)-2-(4-Chlorophenyl)ethenyl]sulfonyl}-N2-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide;
 N2-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N2-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide ;
 N-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-
- 20 oxoethyl]-2-oxopyrrolidin-3-yl}glycine;
 (E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)ethenesulfonamide;
- 25 Methyl N-[(E)-2-(4-chlorophenyl)ethenyl]sulfonyl}-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinate;
 N-[(E)-2-(4-Chlorophenyl)ethenyl]sulfonyl}-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}glycine;
 N-((3S)-1-[(1S)-2-(3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-
- 30 chloronaphthalene-2-sulfonamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-thiomorpholin-4-ylethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}prop-2-ynamide;
- 35 N1-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-N2,N2-dimethylglycinamide;
 Methyl 3-({1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-3-oxopropanoate;
 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-
- 40 yl)propanoyl]piperidin-3-yl}nicotinamide;

- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl}pyridine-2-carboxamide;
 6-Chloro-N-ethyl-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 5 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(5-oxo-1,4-diazepan-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 10 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 15 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-[(2-methyl-1,3-thiazol-4-yl)methyl]naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(pyridin-2-ylmethyl)naphthalene-2-sulfonamide formate;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-
- 20 (pyridin-4-ylmethyl)naphthalene-2-sulfonamide formate;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]-N-[(2-methyl-1,3-thiazol-4-yl)methyl]naphthalene-2-sulfonamide formate;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]-N-(pyridin-4-ylmethyl)naphthalene-2-sulfonamide formate;
- 25 N-[(5'-Chloro-2,2'-bithien-5-yl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycine;
 N-[1-((2R)-2-[(3S)-3-[(6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-yl]benzamide;
- 30 6-Chloro-N-(3,3-dimethyl-2-oxobutyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
tert-Butyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinate;
 N-Allyl-6-chloro-N-{1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-
- 35 yl}naphthalene-2-sulfonamide ;
 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-(1-{1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine formate;
 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]glycine;

- 6-Chloro-N-methyl-N-[(3R)-1-[(1R)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-(1-{1-methyl-2-oxo-2-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl}-2-oxopyrrolidin-3-yl)glycine formate ;
 5 (E)-2-(5-Chlorothien-2-yl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]ethenesulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)-1-benzothiophene-2-sulfonamide;
 N2-[(6-Chloro-1-benzothien-2-yl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 10 6-Chloro-N-[(3S)-1-[(1S)-2-[(1R,5S)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-[(1R,5S)-7-[2-(methylamino)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 15 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-[(1R,5S)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide trifluoroacetate;
 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide formate;
 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 20 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-4-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 25 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-(4-methyl-5-oxo-1,4-diazepan-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 N2-[(6-Chloro-2-naphthyl)sulfonyl]-N2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-(2-pyridin-3-ylpyrrolidin-1-yl)ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-morpholin-4-ylethyl)naphthalene-2-sulfonamide formate;
 30 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]-N-(2-pyrrolidin-1-ylethyl)naphthalene-2-sulfonamide formate;
 6-Chloro-N-[2-(dimethylamino)ethyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide formate;
 35 N-[2-[(6-Chloro-2-naphthyl)sulfonyl][(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]amino)ethyl]acetamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 40

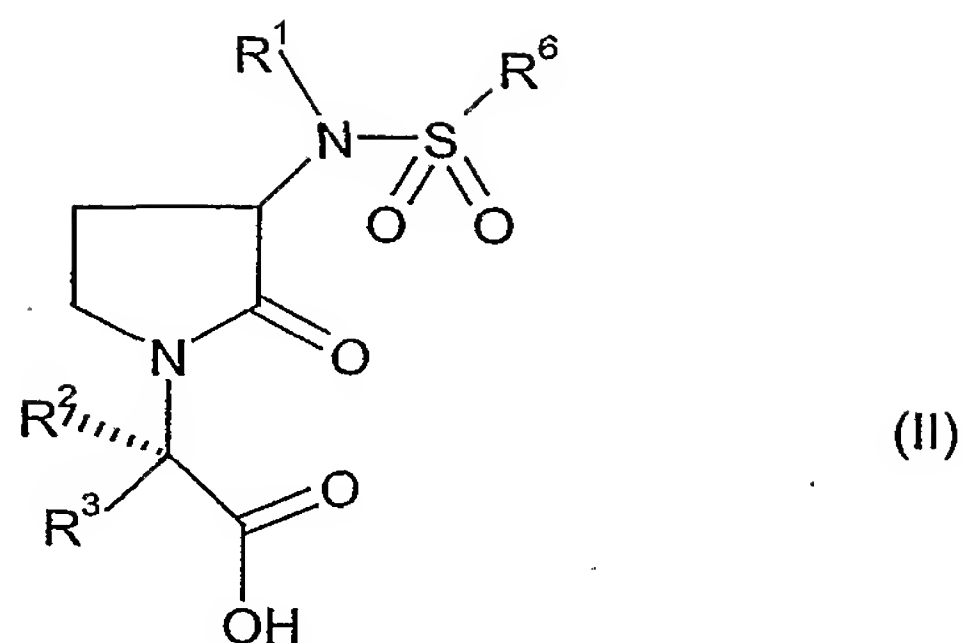
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide formate;
- 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 5 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- 5'-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 10 5'-Chloro-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-2,2'-bithiophene-5-sulfonamide;
- Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)glycinate;
- 15 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)-2,2'-bithiophene-5-sulfonamide;
- N-((3S)-1-[(1S)-2-(3-Aminopiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide;
- (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 20 Methyl N-([(E)-2-(4-chlorophenyl)ethenyl]sulfonyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)glycinate;
- (E)-2-(4-Chlorophenyl)-N-(cyanomethyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)ethenesulfonamide;
- 25 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-((1S)-2-[3-(hydroxymethyl)piperidin-1-yl]-1-methyl-2-oxoethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}acetamide;
- 30 6-Chloro-N-((3S)-1-((1S)-1-methyl-2-oxo-2-[3-(1H-pyrrol-1-ylmethyl)piperidin-1-yl]ethyl)-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 6-Chloro-N-((3S)-1-[(1S)-2-(3,3-dimethylpiperidin-1-yl)-1-methyl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
- 35 N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}prop-2-ynamide;
- N-{1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl}-1-methyl-1H-pyrrole-3-carboxamide;
- Methyl 4-({1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl]propanoyl}piperidin-3-yl)amino)-4-oxobutanoate;
- 40

- 4-({1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino}-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-4-oxobutanoic acid;
 N-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide;
 5 N-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}pyridine-2-carboxamide;
 N-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}isonicotinamide;
 Methyl 3-((3S)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}amino)-3-oxopropanoate;
 10 N-1-((3S)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}-N-2,N-2-dimethylglycinamide;
 Benzyl (3R)-1-[(2S)-2-((3S)-3-[(6-chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-ylcarbamate;
 15 N-((3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}nicotinamide;
 N-((3R)-1-[(2S)-2-((3S)-3-[(6-Chloro-2-naphthyl)sulfonyl]amino)-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl}isonicotinamide;
 5'-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-2,2'-
 20 bithiophene-5-sulfonamide ;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1-benzothiophene-2-sulfonamide;
 (E)-2-(4-Chlorophenyl)-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide;
 25 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1-benzothiophene-2-sulfonamide compound with 4-chloro-N-((3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl)-1-benzothiophene-2-sulfonamide (1:1);
 6-Chloro-N-(3-furylmethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 30 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(pyridin-3-ylmethyl)naphthalene-2-sulfonamide formate;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(2-oxobutyl)naphthalene-2-sulfonamide;
 N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}glycinamide;
 35 6-Chloro-N-(2-furylmethyl)-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)naphthalene-2-sulfonamide;
 6-Chloro-N-((3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl)-N-(1,3-thiazol-2-ylmethyl)naphthalene-2-sulfonamide;

- Methyl N-[(5'-chloro-2,2'-bithien-5-yl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinate;
- 5'-Chloro-N-(cyanomethyl)-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-2,2'-bithiophene-5-sulfonamide;
- 5 6-Chloro-N-[(3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-[(3R)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 6-Chloro-N-methyl-N-[(3S)-1-[(1R)-1-methyl-2-(3-methylpiperidin-1-yl)-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 10 N-[1-((2R)-2-[(3S)-3-[(6-chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl)propanoyl]piperidin-3-yl]acetamide;
- 6-Chloro-N-(cyanomethyl)-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 15 6-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- N-Allyl-6-chloro-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycinate;
- 20 N-[(6-Chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl]glycine;
- 6-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- 25 6-Chloro-N-methyl-N-[(3S)-1-[(1S)-1-methyl-2-[(2R)-2-methylpiperidin-1-yl]-2-oxoethyl]-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
- Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinate;
- N-[(6-Chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycine;
- 30 N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-piperidin-1-ylethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)naphthalene-2-sulfonamide;
- 35 N-2-[(6-Chloro-2-naphthyl)sulfonyl]-N-2-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]glycinamide;
- Methyl N-[(6-chloro-2-naphthyl)sulfonyl]-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]glycinate formate;
- 6-Chloro-N-[(3S)-1-[(1S)-1-methyl-2-oxo-2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]ethyl]-2-oxopyrrolidin-3-yl]-N-(2-oxobutyl)naphthalene-2-sulfonamide;
- 40

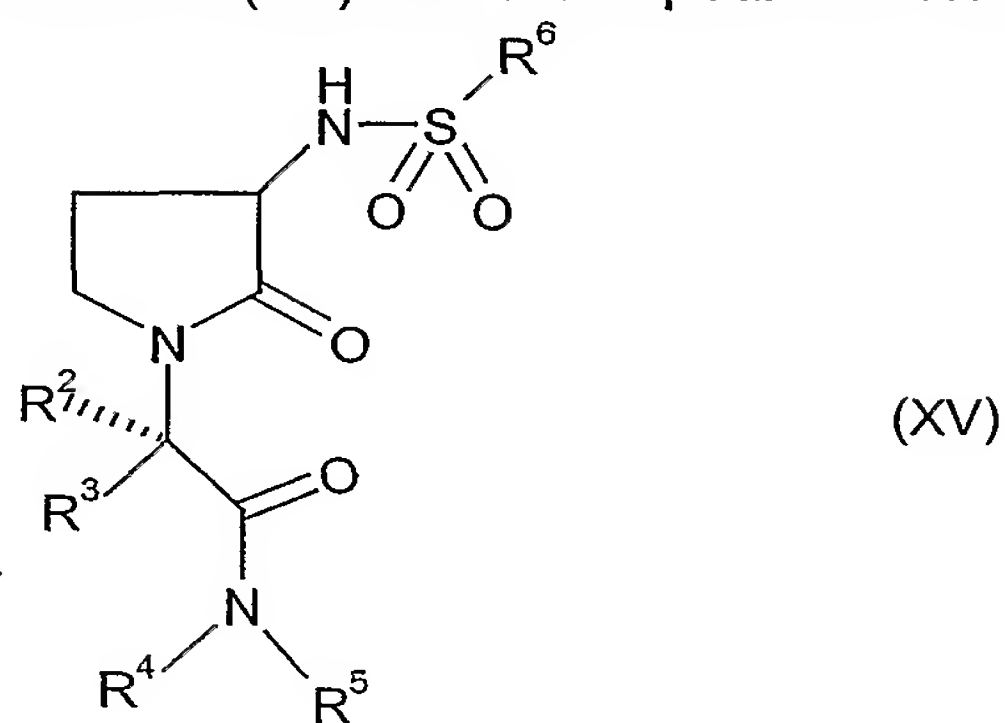
- N-[1-((2R)-2-((3S)-3-[[[6-Chloro-2-naphthyl)sulfonyl](methyl)amino]-2-oxopyrrolidin-1-yl]propanoyl)piperidin-3-yl]benzamide;
 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1H-pyrrol-2-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 5 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(pyridin-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 6-Chloro-N-[(3S)-1-((1S)-1-methyl-2-oxo-2-{3-[(1H-pyrazol-3-ylmethyl)amino]piperidin-1-yl}ethyl)-2-oxopyrrolidin-3-yl]naphthalene-2-sulfonamide;
 Benzyl (3S)-1-[(2S)-2-((3S)-3-[[[6-chloro-2-naphthyl)sulfonyl]amino]-2-oxopyrrolidin-1-yl]propanoyl]piperidin-3-ylcarbamate;
 10 N-((3S)-1-{(1S)-2-[(3S)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl}-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide; and
 N-((3S)-1-{(1S)-2-[(3R)-3-Aminopiperidin-1-yl]-1-methyl-2-oxoethyl}-2-oxopyrrolidin-3-yl)-6-chloronaphthalene-2-sulfonamide.
 15
11. A compound according to any one of claims 1-10 for use in therapy.
12. A pharmaceutical composition comprising a compound according to any one of claims 1-10 together with a pharmaceutical carrier and/or excipient.
 20
13. Use of a compound according to any one of claims 1-10 for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.
- 25 14. A method of treating a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor comprising administering a therapeutically effective amount of a compound according to any one of claims 1-10.
15. A process for preparing a compound of formula (I) which comprises:
 30 (a) reacting a compound of formula (II) with a compound of formula (III):

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OR:

(b) reacting a compound of formula (XV) with a compound of formula (VI):

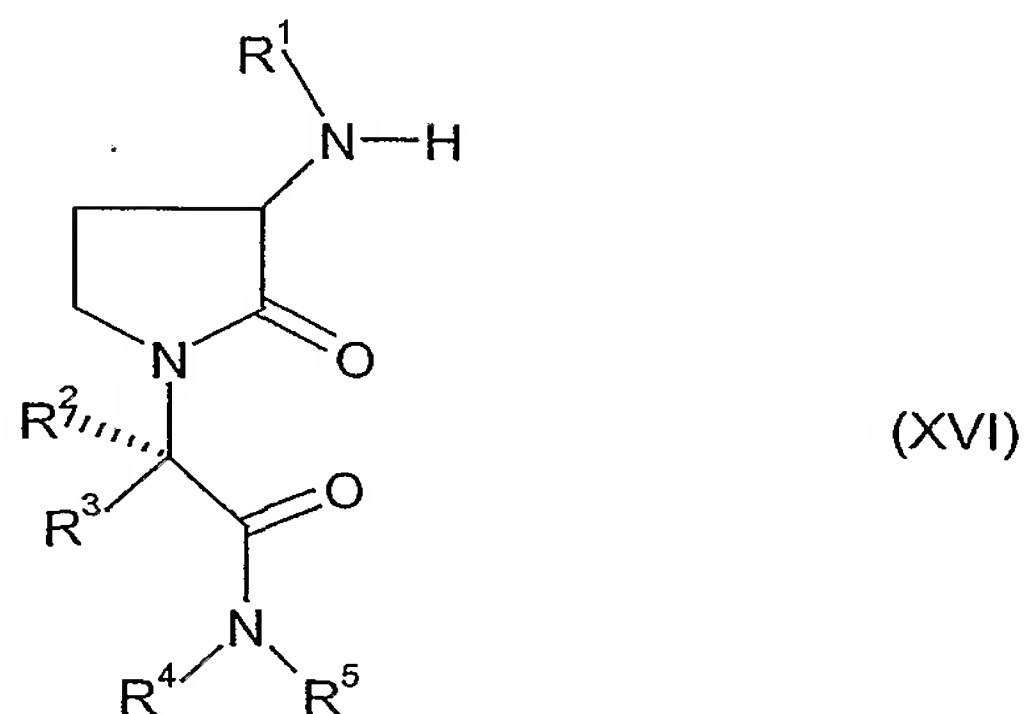


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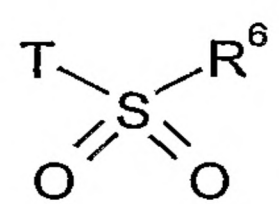


OR:

10 (c) reacting a compound of formula (XVI) with a compound of formula (VIII):



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(VIII)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02586

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K5/06 A61K31/4025 A61K31/454 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 39759 A (AVENTIS PHARMA DEUTSCHLAND GMBH, GERMANY) 7 June 2001 (2001-06-07) the whole document ---	1-15
A	WO 00 47563 A (BRISTOL MYERS SQUIBB CO) 17 August 2000 (2000-08-17) claims; example 19 ---	1-15
A	WO 98 16523 A (COR THERAPEUTICS INC) 23 April 1998 (1998-04-23) page 26, line 1-10; claims ---	1-15
A	WO 93 01208 A (BASF A.-G., GERMANY) 21 January 1993 (1993-01-21) the whole document -----	1-15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

2 September 2002

Date of mailing of the international search report

10/09/2002

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/02586

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0139759 9 A		NONE	
WO 0047563 A	17-08-2000	AU 2630000 A	29-08-2000
		EP 1175405 A1	30-01-2002
		WO 0047563 A1	17-08-2000
		US 6344450 B1	05-02-2002
WO 9816523 A	23-04-1998	US 6262047 B1	17-07-2001
		AU 720513 B2	01-06-2000
		AU 4980997 A	11-05-1998
		EP 0937073 A2	25-08-1999
		JP 2001504810 T	10-04-2001
		WO 9816523 A2	23-04-1998
WO 9301208 A	21-01-1993	DE 4121947 A1	07-01-1993
		AT 166065 T	15-05-1998
		CA 2112580 A1	21-01-1993
		DE 59209327 D1	18-06-1998
		DK 668869 T3	07-10-1998
		WO 9301208 A1	21-01-1993
		EP 0668869 A1	30-08-1995
		ES 2115673 T3	01-07-1998
		JP 6509076 T	13-10-1994
		MX 9203910 A1	01-01-1993
		US 5489583 A	06-02-1996

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/GB 02/02586

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.